RING-OPENING BENZANNULATIONS OF CYCLOPROPENES, ALKYLIDENE CYCLOPROPANES AND 2,3-DIHYDROFURAN ACETALS: A COMPLEMENTARY APPROACH TO BENZO-FUSED (HETERO)AROMATICS

A Dissertation
Presented to
The Academic Faculty

By

Joel Aponte-Guzmán

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy in the
School of Chemistry and Biochemistry

Georgia Institute of Technology
December 2015

RING-OPENING BENZANNULATIONS OF CYCLOPROPENES, ALKYLIDENE CYCLOPROPANES AND 2,3-DIHYDROFURAN ACETALS: A COMPLEMENTARY APPROACH TO BENZO-FUSED (HETERO)AROMATICS

Approved by:

Dr. Stefan France, Advisor
School of Chemistry & Biochemistry
Georgia Institute of Technology

Dr. David M. Collard
School of Chemistry & Biochemistry
Georgia Institute of Technology

Dr. Christoph J. Fahrni
School of Chemistry & Biochemistry
Georgia Institute of Technology

Dr. Christopher W. Jones
School of Chemical & Biomolecular Enginnering
Georgia Institute of Technology

Dr. Adegboyega Oyelere
School of Chemistry & Biochemistry
Georgia Institute of Technology

Date Approved: November 5th, 2015.

This thesis is dedicated to my mother, Gladys Guzmán-Matos, as well as all my siblings Jonaldys Aponte-Guzmán, Raymond J. Esteves-Guzmán, and Izamar Rivera-Guzmán for all the support and love provided during my development as a person and as a scientist.

ACKNOWLEDGEMENT

This work was possible thanks to the help of several professors, graduate students and undergraduate students. Thanks to Dr. Stefan France for the guidance and support during the PhD program. Dr. Leslie Gelbaum, your help on the NMR training and interpretation was indispensable. The knowledge contributed by the former graduate students Lien H. Phun and Marchello A. Cavitt is also well appreciated; without them, the final outcome of this work was not going to be the same. Special thanks to the undergraduate students Jack C. David, Elayna Tillman, and particularly John E. Taylor, Jr. for investing your precious time working with me.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

^{1}H	Proton NMR
^{13}C	Carbon NMR
AcOH	Acetic acid
AgOTf	Silver (I) Trifluoromethanesulfonate
ACP	Alkylidene Cyclopropane
$AlCl_3$	Aluminum (III) Chloride
$Al(OTf)_3$	Aluminum (III) Trifluoromethanesulfonate
ATR	Attenuated total reflectance
$BF_3.Et_2O$	Boron trifluoride diethyl etherate
BRSM	Based on recovered starting material
bs	Broad singlet
n-BuLi	*n*-Butyllithium
t-BuLi	*tert*-Butyllithium
C_6H_6	Benzene
CaH_2	Calcium Hydride
$CDCl_3$	Deuterated chloroform
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
$(COCl)_2$	Oxalyl chloride
$Cu(OTf)_2$	Copper (II) Trifluoromethanesulfonate
d	Doublet
dd	Doublet of doublets

dd	Doublets of doublets of doublets
Et_3N	Triethylamine
Et_2O	Diethyl ether
D-A	Donor-acceptor
DA	Diels Alder
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DMSO-d_6	Deuterated dimethylsulfoxide
DMSO	Dimethylsulfoxide
Et_3N	Triethylamine
EtOH	Ethanol
EWG	Electron withdrawing group
FTIR	Fourier Transform Infrared
H_2O	Water
HBr	Hydrobromic acid
HCl	Hydrochloric acid
H_2SO_4	Sulfuric Acid
Hz	Hertz
$In(OTf)_3$	Indium (III) trifluoromethanesulfonate
$InCl_3$	Indium (III) trichloride iPr Isopropyl
K_2CO_3	Potassium carbonate

KOH	Potassium hydroxide
LA	Lewis acid
LDA	Lithium diisopropylamide
$LiAlH_4$	Lithium aluminum hydride
LiHMDS	Lithium hexamethyldisilazide
LiOH	Lithium hydroxide
MeCN	Acetonitrile
$MeNO_2$	Nitromethane
MeOAc	Methyl acetate
MeOH	Methanol
$Mg(OTf)_2$	Magnesium trifluoromethanesulfonate
4 A MS	4 A Molecular sieves
N_2	Nitrogen
Na_2CO_3	Sodium carbonate
PAA	p-Anisaldehyde
PPA	Polyphophoric acid
p-TSA	p-Toluenesulfonic acid
PPTS	Pyridinium para-toluenesulfonate
RCM	Ring-closing methatesis
$Rh_2(esp)_2$	Dirhodium α,α,α',α'-tetramethyl-1,3-benzenedipropanoate
$Rh_2(OAc)_4$	Rhodium acetate dimer
$Rh_2(oct)_4$	Rhodium octonate dimer
$Rh_2(S\text{-}PTAD)_4$	Tetrakis[(S)-(1-adamantyl)-(N-phthalimido)acetato]dirhodium(II)

rt	Room temperature
$SnCl_4$	Tin (IV) chloride
$Sc(OTf)_3$	Scandium (III) trifluoromethanesulfonate
t	Triplet
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TsN_3	Toluenesulfonylazide
$Yb(OTf)_3$	Ytterbium (III) trifluoromethanesulfonate
2,3-DHF	2,3-Dihydrofuran

SUMMARY

Benzo-fused biaryl and heterobiaryl compounds are common structural elements found in high value molecules such as bioactive natural products, pharmaceuticals, agrochemicals, conducting polymers, and organic dyes. Moreover, *o*-phenolic esters and compounds containing a naphthol moiety can serve as versatile chiral ligands in synthetic organic chemistry, whereas benzofuran natural products and indole alkaloids have shown an enormous potential as pharmacological agents. Given the predominance and diverse utility of benzo-fused heteroaromatics and indole alkaloids, the development of efficient methodologies to access these core structures has become an important goal for synthetic chemists.

Herein we describe three complementary methodologies to access benzo-fused biaryl and heterobiaryl compounds from cyclopropenes, alkylidene cyclopropanes and 2,3-dihydrofuran acetals. When submitted to catalytic Lewis acid conditions, these intermediates underwent ring-opening cyclizations to form the corresponding functionalized arenes in good to high yields (up to 98%). These ring-opening cyclizations can be employed in a complementary manner to access a large and diverse scope of functionalized benzenoid compounds, with potential application in the synthesis of bioactive molecules.

To further exploit the great potential of the ring-opening cyclizations, we were also interested in developing industrially-viable flow technologies toward the multi-step synthesis of fused-indole alkaloid frameworks. Under optimized conditions, hydropyrido[1,2-*a*]indoles were synthesized using a continuous flow tandem reactor with excellent conversions, yields and throughputs. This represents the first example of cyclopropanation/homo-Nazarov-type

cyclizations in continuous flow and carries promising results towards a multi-step continuous flow synthesis of hydropyrido[1,2-*a*]indoles with further industrial applications.

CHAPTER 1

INTRODUCTION: IMPORTANCE OF BENZANNULATED (HETERO)AROMATIC COMPOUNDS AND RELEVANT BENZANNULATION REACTIONS

1.1 Statement of Purpose

Heterocyclic compounds, including heteroaromatics, make up for more than one-half of all known molecules.[1] These essential scaffolds are not only present in different biological metabolism pathways but also exist in a large pool of natural/unnatural bioactive molecules, as well as commercially relevant products. Thus, the development of efficient synthetic methods to access heterocyclic compounds has been precedent in the literature and still represents a very active area of current research. More specifically, the assembly of polysubstituted benzo-fused (hetero)aromatics is highly important in modern organic chemistry due to their prevalence in natural products and materials science.[1-3]

Benzannulation represents an important strategy in organic synthesis for the assemblage of benzo-fused polycycles.[4] Here we disclose three 'complementary' intramolecular ring-opening benzannulations to access a large array of functionalized (hetero)aromatic scaffolds. Besides the novelty of the methodologies, these benzannulation reactions aim to open the synthetic door to a handful of bioactive natural products as well as providing different points for easy functionalization by using the same preparation methods to access the starting materials (hence the term 'complementary'). Also, as part of our interest in providing the scientific community with industrial methods for rapid scale-up, we used the chemistry developed in our laboratory to establish a tandem, bicatalytic continuous

flow cyclopropanation/ring-opening cyclization protocol to access hydropyrido[1,2-*a*]indoles in a multi-gram scale.

1.2 Heterocycles, Heteroaromatics, and Arenes

1.2.1 Relevance

Heterocycles comprise the basic building blocks for many biologically important molecules as well as other common structural elements found in bioactive natural products, pharmaceuticals, agrochemicals, conducting polymers, and organic dyes.[1-3] Particularly, their role in the design of therapeutic molecules can be shown when over 80% of the top small-molecule drugs by US retail sales in 2010 contain at least one heterocyclic fragment in their structures (Figure 1-1).[1]

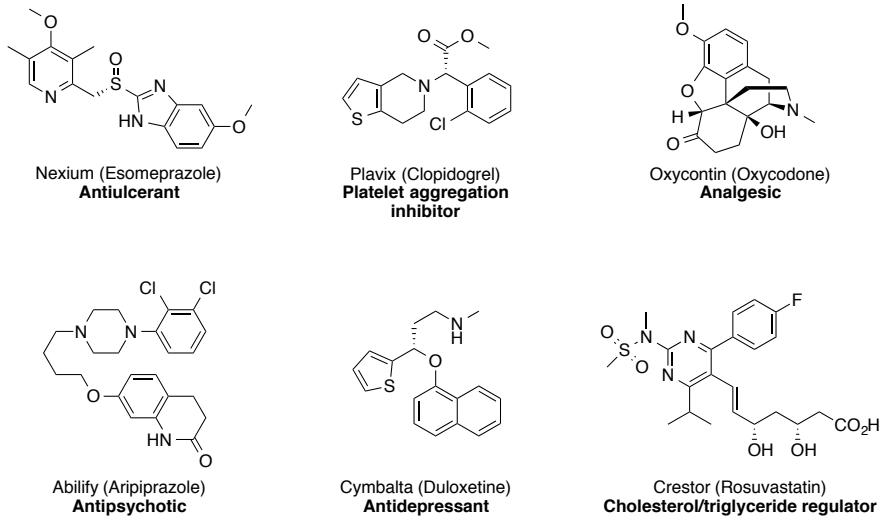


Figure 1-1. Selected top small molecule drugs in US.

Functionalized aromatic heterocycles (or heteroaromatics) and other aromatic benzenoid compounds also play a pivotal role in organic synthesis and medicinal chemistry.

For example, benzofurans[3b] and benzothiophenes[3c] have shown potential applications in medicinal chemistry and materials science;[5] meanwhile, indole alkaloids are present in a large variety of bioactive natural products[6] (Figure 1-2). Moreover, naphthols and *o*-phenolic esters can serve as versatile chiral ligands in synthetic organic chemistry.[7] The predominance and diverse utility of benzo-fused (hetero)aromatics have increased the interest towards the development of efficient syntheses, becoming an important goal of synthetic chemists.

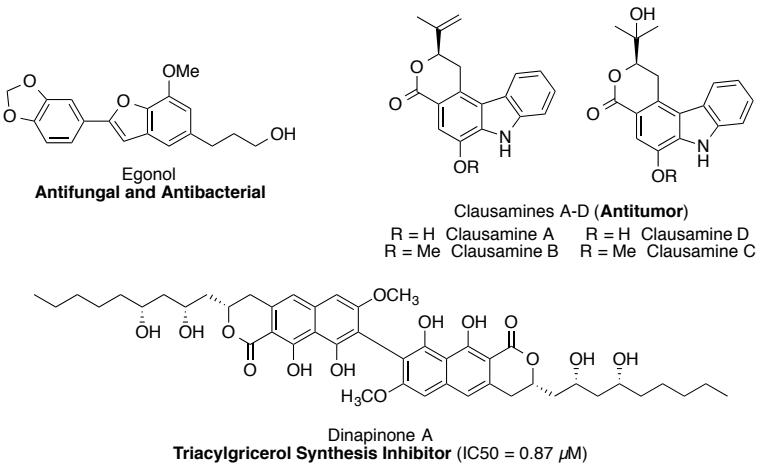


Figure 1-2. Examples of bioactive benzenoid natural products.

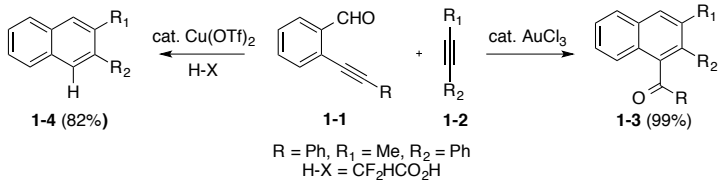
1.2.2 Relevant benzannulation reactions

Over the past decades, functional group manipulation of aromatic precursors has been a common strategy to access new aromatic compounds. However, these classical methods, such as Friedel-Crafts alkylations and electrophilic/nucleophilic aromatic substitutions, have shown lack of regioselectivity besides the use of activators in excess amounts.[8] To this end, numerous benzannulations to form benzo-fused substrates via Diels-Alder (DA), ring-closing metathesis (RCM), cycloaddition, and transition-metal-promoted processes have been reported.[4] Appending a benzene ring directly onto a pre-existing ring is preferable to many

classical methods due to the likely reduction of reaction steps and superior regiocontrol. However, many of these benzannulation reactions require air- and/or moisture- sensitive reaction conditions, a last oxidation step, or the use of highly functionalized precursors. Here, a condensed review on benzannulation reactions is presented.

1.2.2.1 Benzannulation via Diels-Alder reaction

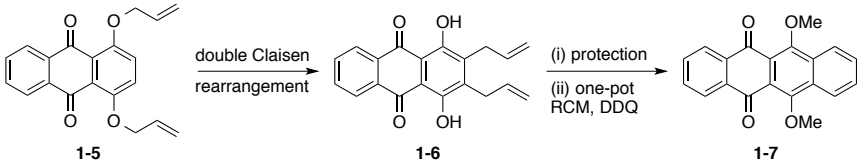
The Diels-Alder (DA) cycloaddition is a well-used transformation due to its high regiochemistry control when reacting a substituted diene and dienophile. For this reason, the synthesis of several polycyclic aromatic compounds using the DA reaction has been reported.[9] For example, Yamamoto and co-workers found that naphtyl ketone derivative **1-3** was made when enynal [*o*-(alkynyl)benzaldehyde] **1-1** reacted with alkyne **1-2** in the presence of catalytic amounts of $AuCl_3$. In contrast, the decarbonylated naphthalene derivative **1-4** was formed selectively when using catalytic $Cu(OTf)_2$ and stoichiometric amounts of Brønsted acid (Scheme 1-1).[10] Also, various benzannulated indane- and fullerene-based α-amino acid derivatives as well as benzene ring-fused annulenes have been synthesized using the DA approach as a key step.[11]



Scheme 1-1. Yamamoto's reported Diels-Alder benzannulations.

1.2.2.2 Benzannulation via ring-closing metathesis (RCM)

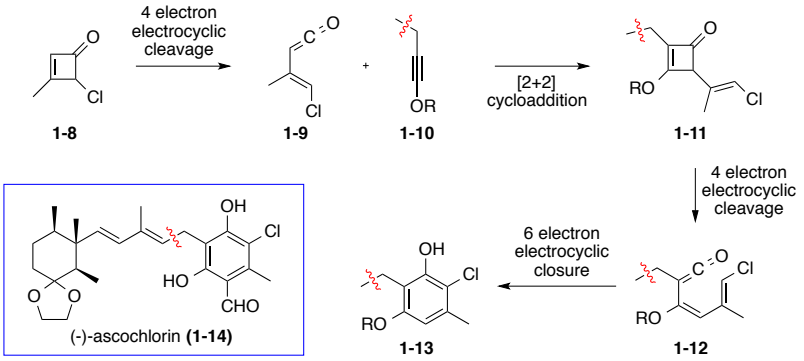
Ring-closing metathesis (RCM) is a powerful strategy for the synthesis of simple and complex cyclic compounds from acyclic dienes. Thus, using Grubbs and Schrock catalysts, a wide variety of carbo- and heterocyclic compounds have been prepared under mild reaction conditions and with high functional group tolerance.[12] This [2+2] cycloaddition/cycloreversion approach has also been extended to the preparation of aromatic compounds. As an example, Kotha and Mandal described a benzannulation using a double Claisen rearrangement followed by a one-pot RCM and DDQ oxidation sequence to form tetraquinone derivative **1-7** (Scheme 1-2).[13] Other important scaffolds, such as phenanthrene, dibenzanthracene, carbazole, and indole derivatives have also been synthesized using RCM as a main or key step.[4]



Scheme 1-2. Benzannulation via one-pot RCM/DDQ oxidation

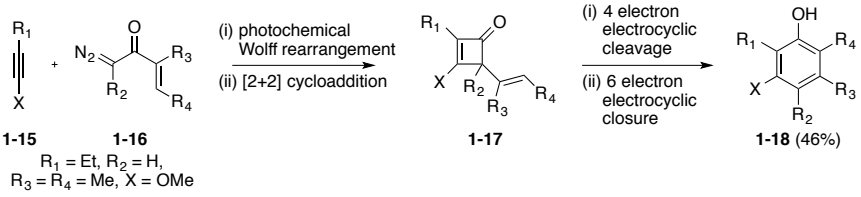
1.2.2.3 Benzannulation via Danheiser protocol

The Danheiser benzannulation is a regiocontrolled formation of phenols in a single step from the combination of cyclobutenones (such as **1-8**) and hetero-substituted acetylenes (such as **1-10**). This strategy was used by Danheiser and co-workers to construct (-)-ascochlorin (**1-14**), a natural product that exhibits antiviral, antibiotic and antitumour activities.[14] The regioselectivity of this process is determined by the regiospecific [2+2] cycloaddition between ketene **1-9** and an acetylene derivative **1-10** (Scheme 1-3).



Scheme 1-3. Formation of phenols via the Danheiser benzannulation.

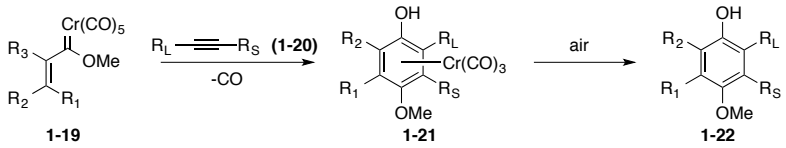
A modified Danheiser benzannulation (or second generation Danheiser benzannulation) has also been reported. In this case, a photochemical Wolff rearrangement of an unsaturated α-diazo ketone **1-16** generates an aryl or vinylketene, which reacts with acetylene **1-15** to produce cyclobutenone **1-17** (Scheme 1-4).[15a] After a series of ring-opening and ring-closing electrocyclic reactions, phenol **1-18** is formed. Both, the first and second generation Danheiser benzannulations are capable of producing a range of highly substituted phenols, naphthalenes, benzofurans, benzothiophenes and indoles. Using this metholology, a series of natural products has also been synthesized.[15b-d]



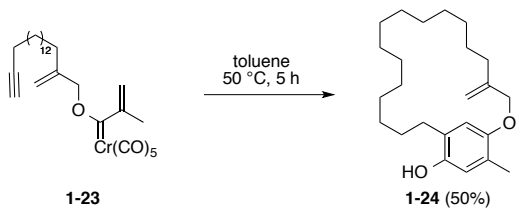
Scheme 1-4. Formation of phenols via the 2nd generation Danheiser benzannulation.

1.2.2.4 Benzannulation via Dötz protocol

Highly functionalized aromatic rings can also be constructed using the Dötz benzannulation. This protocol proceeds through a [3+2+1] cycloaddition of an aromatic or vinylic alkoxy pentacarbonyl chromium carbene complex (**1-19**) with an alkyne (**1-20**) and carbon monoxide to give phenol (**1-22**) after exposure to air (Scheme 1-5). The regioselectivity is determined by the size of the substituents on the alkyne. This protocol is one of the most used transition-metal-promoted benzannulations for the formation of highly-functionalized phenols[16] and has also been applied to the construction of large-ring systems (Scheme 1-6), as shown recently by Nakata.[17]



Scheme 1-5. Generation of phenols via Dötz benzannulation.

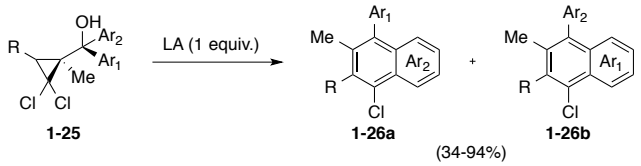


Scheme 1-6. Generation of large-ring systems via Dötz benzannulation.

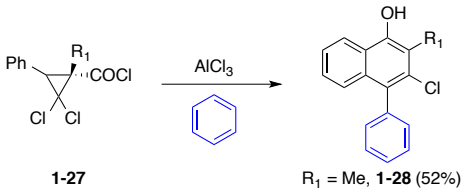
1.2.2.5 Benzannulation via Lewis acid-catalyzed cyclization

Cyclopropanes have also played a role in benzannulation reactions. Nishi and co-workers reported the synthesis of highly substituted α-arylnaphthalenes (**1-26a** or **1-26b**) from aryl-(2,2-dichlorocyclopropyl)methanols **1-25** via a Lewis acid-promoted ring

expansion, followed by an intramolecular Friedel-Crafts reaction (Scheme 1-7). The regioselectivity of the reaction products depends on the Lewis acid used due to the ability of MCl_4 (M = Sn, Ti) to go through a chelation mechanism versus a non-chelated mechanism using TMSOTf.[18] In a separate report, when 3-aryl-2,2'-dihalocyclopropanecarbonyl chlorides **1-27** were submitted to Lewis acid in the presence of substituted benzenes, 4-aryl-1-naphthols **1-28** were synthesized in moderate yields (Scheme 1-8).[19]



Scheme 1-7. Synthesis of α-arylnaphthalenes via Lewis-acid promoted benzannulation.



Scheme 1-8. Synthesis of 4-aryl-1-naphthols via Lewis-acid promoted benzannulation.

1.2.2.6 Other benzannulation reactions

Benzo-fused (hetero)aromatic compounds have also been synthesized utilizing other benzannulation reactions such as cycloaddition tactics, base-induced rearrangements, photo-induced cyclizations, transition-metal-promoted processes, or through other methods not mentioned above. For a better understanding on benzannulation reactions see the cited reviews.[4]

1.3 Benzannulations of Cyclopropenes, Alkylidene Cyclopropanes, and 2,3-Dihydrofuran O,O- and N,O-Acetals: A Complementary Approach to Benzo-Fused (Hetero)aromatics

As part of our ongoing efforts in studying carbo- and hetero- cycles,[20] we were interested in developing new benzannulations to access a wide array of highly functionalized (hetero)aromatic benzenoid compounds. To this end, three complementary benzannulation procedures were developed, which allow for easy derivatization at different stages of the synthesis and access to different benzenoid regioisomers. These methodologies are considered complementary because of using similar procedures to prepare the starting materials and products. In the presence of Rh(II), α-diazo-β-ketoester compounds (**1-29**) were reacted with alkynes (**1-30**), allenes (**1-33**) or enol ether (or enamides) (**1-35**) to obtain the corresponding cyclopropenes (**1-31**), alkylidene cyclopropanes (ACPs, **1-34**) or 2,3-dihydrofuran acetals (**1-36**), respectively, as three different synthetic intermediates or building blocks (Figure 1-3).

These building blocks were submitted to Lewis acid conditions to promote the ring-opening/benzannulation cascade. More specifically, when submitted to catalytic $In(OTf)_3$, cyclopropenes **1-31** were isomerized to form benzo-fused heteroaromatics (**1-32**) through a ring-opening Friedel-Crafts-type alkenylation, which mode of activation resulted mechanistically different than previously observed.[20c, 21] In the case of ACPs **1-34**, an underexplored system for the intramolecular ring-opening cyclization, a formal homo-Nazarov-type cyclization in the presence of $Yb(OTf)_3$ yielded fully substituted and/or different benzenoid regioisomers (**1-32**).[20d] Lastly, the $Al(OTf)_3$-promoted ring-opening/cyclization/elimination cascade of 2,3-dihydrofuran (2,3-DHF) O,O- and N,O-

acetals **1-36** resulted in a novel transformation to generate *o*-phenolic esters and different regioisomers of benzo-fused aromatics (**1-32**).[22]

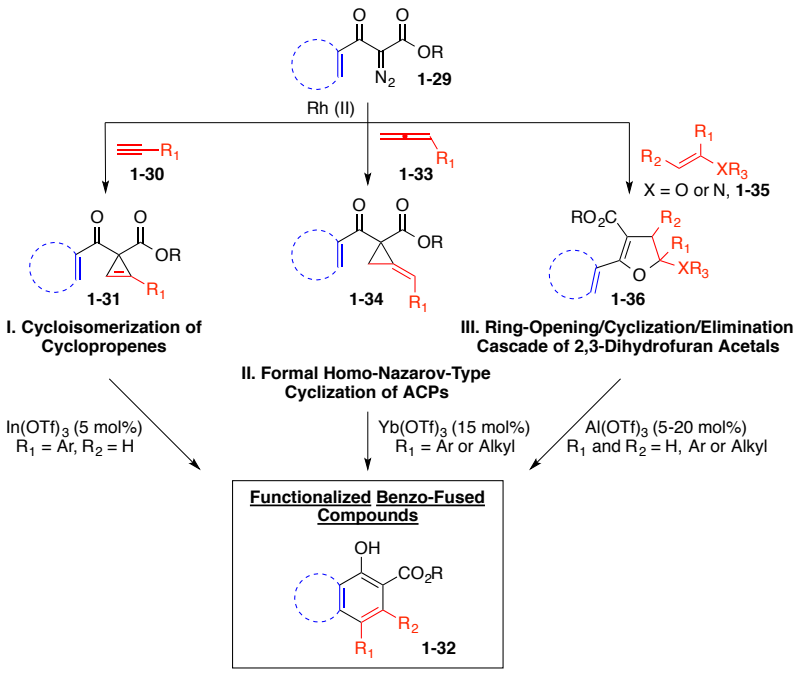
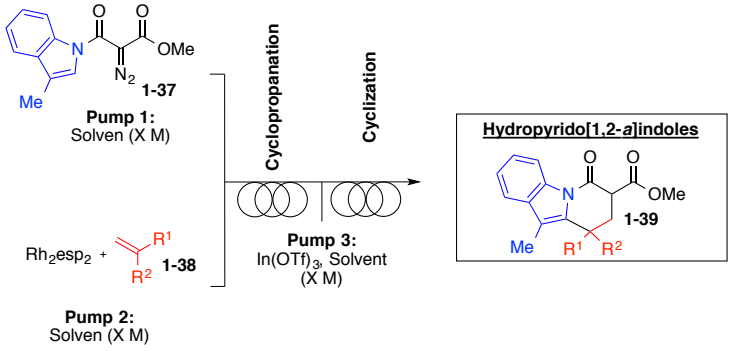


Figure 1-3. Complementary benzannulation protocols from cyclopropenes, alkylidene cyclopropanes and 2,3-dihydrofuran acetals to access an array of highly functionalized benzo-fused compounds.

Due to the large library of known bench stable diazo compounds and the huge availability of carbene-reactive π-systems, the combination of these methodologies can be impactful. By means, these ring-opening benzannulations can be employed in a complementary manner to access a large and diverse scope of functionalized benzenoid compounds, with a potential impact on the synthesis of bioactive molecules.

1.4 A Contribution to Industrial Processes: A Tandem, Bicatalytic Continuous Flow Cyclopropanation/Ring-Opening Cyclization

Historically, batch processing has been the major strategy in the synthesis of complex molecules, especially molecules of pharmaceutical interest. In general, this approach has been fraught with high cost, excessive time for scale-up, and waste issues. Alternatively, continuous flow technology has been identified as a production vehicle since it has both environmental and economic advantages. Continuous flow technology offers superior mass and heat transfer, and lower production costs when compared with the traditional batch technology.[23] Herein, we take advantage of continuous flow technology to conduct the multi-step synthesis of the hydropyrido[1,2-*a*]indoles **1-39**, a skeleton present in many naturally occurring indole alkaloids and pharmaceutically relevant compounds (Scheme 1-9).[24]



Scheme 1-9. Tandem, bicatalytic continuous flow ring-opening cyclization to access hydropyrido[1,2-*a*]indoles.

1.5 References

1. a) Gomtsyan, A. *Chemistry of Heterocyclic Compounds* **2012**, *48*, 7-10; b) Han, C.; Zhang, J.; Zheng, M.; Xiao, Y.; Li, Y.; Liu, G. *Mol. Diversity* **2011**, *15*, 857-876.

2. a) Senthil Kumar, N.; Clement, J. A.; Mohanakrishnan, A. K. *Tetrahedron* **2009**, *65*, 822; b) Li, H.; Sun, S.; Salim, T.; Bomma, S.; Grimsdale, A. C.; Lam, Y. M. *J. Polym. Sci. Part A* **2012**, *50*, 250.

3. a) Rodriguez, D.; Castedo, L.; Dominguez, D.; Saa, C. *Org. Lett.* **2003**, *15*, 3119-3121; b) Abu-Hashem, A. A.; Hussein, H. A.; Aly, A. S.; Gouda, M. A. *Synthetic Communications*, **2014**, *44*, 2285; c) Ming, W.; Liu, X.; Wang, L.; Liu, J.; Wang, M. *Org. Lett.* **2015**, *17*, 1746-1749.

4. For reviews on benzannulations, see: a) Kotha, S.; Misra, S.; Halder, S. *Tetrahedron* **2008**, *64*, 10775-10790; b) Rubin, M.; Sromek, A. W.; Gevorgyan, V. *Synlett* **2003**, 2265-2291; c) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901-2915.

5. a) Hsu, D.-T.; Lin, C.-H. *J. Org. Chem.* **2009**, *74*, 9180-9187; b) Kumar, N. S.; Mohanakrishnan, A. K. *Tetrahedron* **2010**, *66*, 5660-5670; c) Mohanakrishnan, A. K.; Amaladass, P.; Arul, C. J. *Tetrahedron Lett.* **2007**, *48*, 779-784.

6. a) Bronner, S. M.; Im, G.-Y. J.; Garg N. K. in *Heterocycles in Natural Product Synthesis* (Eds.: Majumdar, K. C.; Chattopadhyay, S. K.), Wiley-VCH, Weinheim, Germany, **2011**, pp. 221-265; b) Juwarker, H.; Suk, J.-m.; Jeong, K.-S. *Top. Heterocycl. Chem.* **2010**, *24*, 177-204; c) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195-7210; d) Vicente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469-6480.

7. Panda, N.; Mothkuri, R.; Pal, A.; Paital, A. *Adv. Synth. Catal.* **2013**, *355*, 2809.

8. Smith, K.; El-Hiti, G. A. *Green Chem.* **2011**, *13*, 1579-1608.

9. Kotha, S.; Chavan, A.; Deepti, G. *ACS Comb. Sci.* **2015**, *17*, 253-302.

10. a) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650-12651; b) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921-10925.

11. a) Kotha, S.; Ghosh, A. K. *Tetrahedron* **2004**, *60*, 10833-10841; b) Kotha, S.; Brahmachary, E. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2719-2722; (c) Kotha, S.; Ganesh, T.; Ghosh, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1755-1757.

12. a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117-7140; b) Kotha, S.; Sreenivasachary, N. *Indian J. Chem.* **2001**, *40B*, 763-780; c) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592-4633.

13. a) Kotha, S.; Mandal, K. *Tetrahedron Lett.* **2004**, *45*, 2585-2589; b) Kotha, S.; Shah, V. R.; Mandal, K. *Adv. Synth. Catal.* **2007**, *349*, 1159-1172.

14. Danheiser, R. L.; Takaki, K.; Cha, D. *Org. Lett.* **2000**, *2*, 3407-3410.

15. a) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Millar, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093-3100; b) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806-810; c) Danheisr, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471-9479; d) Danheiser, R. L.; Casebier, D. S.; Firooznia, F. *J. Org. Chem.* **1995**, *60*, 8341-8350.

16. Watanabe, M.; Tanaka, K.; Saikawa, Y.; Nakata, M. *Tetrahedron Lett.* **2007**, *48*, 203-206.

17. Tanaka, K.; Matsuyama, H.; Watanabe, M.; Fujimori, Y.; Ishibashi, K.; Ozawa, T.; Sato, T.; Saikawa, Y.; Nakata, M. *J. Org. Chem.* **2014**, *79*, 9922-9947.

18. Nishii, Y.; Yoshida, T.; Tanbe, Y. *Tetrahedron Lett.* **1997**, *38*, 7195-7198.

19. Nishii, Y.; Tanbe, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 477-486.

20. a) Phun, L. H.; Patil, D. V.; Cavitt, M. A. *Org. Lett*. **2011**, *13*, 1952; b) Patil, D. V.; Cavitt, M. A.; Grzybowski, P.; France, S. *Chem. Comm.* **2011**, *47*, 10278; c) Phun, L. H.; Aponte-Guzman, J.; France, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3198; d) Aponte-Guzmán, J.; Taylor, J. E., Jr.; Tillman, E.; France, S. *Org. Lett.* **2014**, *16*, 3788; e) Shenje, R.; Williams, C. W.; Francois, K. M.; France, S. *Organic Lett*. **2014**, *16,* 6468; f) Shenje, R.; Martin, M. C.; France, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 13907; g) Martin, M. C.; Patil, D. V.; France, S. *J. Org. Chem.* **2014**, *79*, 3030; h) Cavitt, M. C.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804.

21. Phun, L.; Aponte-Guzmán, J.; France, S. *Synlett* **2012**, *23*, 2723.

22. Aponte-Guzmán, J.; Phun, L.; Taylor, J. E., Jr.; Cavitt, M.; France, S. **2015**, *Manuscript in Preparation.*

23. Malet-Sanz, L.; Susanne, F. *J. Med. Chem.* **2012,** *55*, 4062.

24. Aponte-Guzmán, J.; Shenje, R.; Huang, Y.; Woodham, W. H.; Saunders, S. R.; Mostaghimi, S. M.; Flack, K. R.; Pollet, P.; Eckert, C. E.; Liotta, C. L.; France, S. *Ind. Eng. Chem. Res.* **2015**, *54*, 9550.

CHAPTER 2

BENZANNULATION VIA INDIUM-CATALYZED CYCLOISOMERIZATION OF CYCLOPROPENE-3,3-DICARBONYL COMPOUNDS

The work about to be presented is adapted from a previous publication. My contribution on this project includes, but is not limited to, the synthesis and characterization of the following compounds: cyclopropenes **2-23a**, **2-23f**, and **2-23g**; furans **2-24l**, **2-24r**, **2-24s**, and **2-24t**; and benzo-fused compounds **2-25l** and **2-26g**. For a better understanding on the topic, access the corresponding references.[5,8]

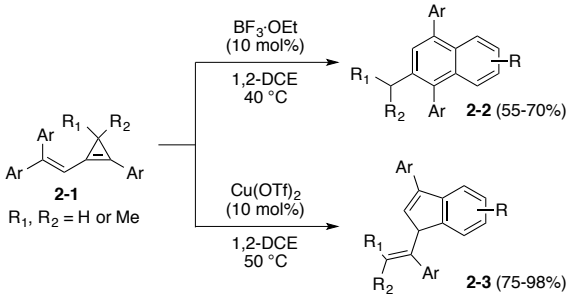
2.1 Introduction

Cyclopropenes, the smallest carbocycles in chemistry, are recognized for their high ring strain. This remarkable strain makes cyclopropenes highly reactive and interesting to study. Moreover, the high *p*-character in the carbon-carbon (C-C) bond and the strong *s*-character of the carbon-hydrogen (C-H) bond in cyclopropenes allow for novel transformations not available to normal olefins, allenes and alkynes. For example, the presence of a double bond allows cyclopropenes to undergo addition transformations (in some cases comparable to olefins), but the liberation of the inherent ring strain enables cyclopropenes to undergo interesting ring-opening transformations. Other types of reactivity include, but are not limited to, an assortment of substitutions, cycloadditions, and metal-promoted transformations.[1]

Cyclopropene cycloisomerizations, usually promoted by transition metals, have dominated the literature due to their ability to construct carbo- and heterocyclic scaffolds

with a high degree of molecular complexity and atom economy. Important scaffolds, such as furans and pyrroles, have been accessed via metallocarbene species generated with Rh (II) or Cu(I) catalyst.[2-4] However, only a few examples of protic- or Lewis acid-catalyzed cycloisomerizations have been reported.[5] Furthermore, Lewis acid-promoted benzannulations via cyclopropene cycloisomerizations are rare in literature.

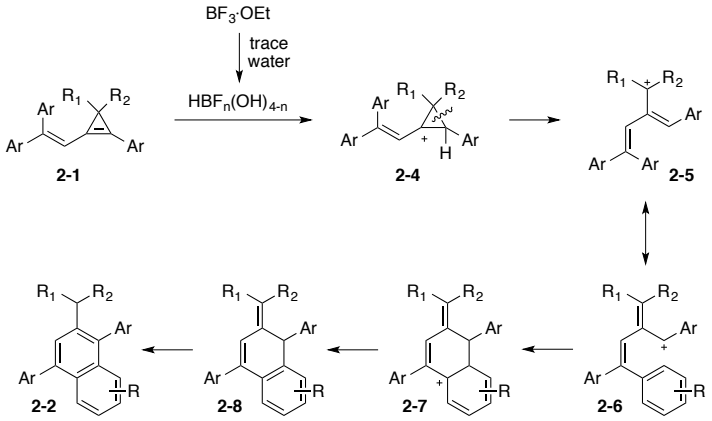
In 2007, Shi and co-workers reported a novel benzannulation reaction under catalytic Lewis acid conditions. Using BF_3·OEt, vinyl cyclopropenes **2-1** were transformed to naphthalene derivatives **2-2** via a Friedel-Crafts rearrangement (Scheme 2-1). The chemoselectivity of the reaction depends on the Lewis acid used. This was shown when the same vinyl cyclopropenes **2-1** resulted in the formation of indenes **2-3** with catalytic $Cu(OTf)_2$.[6]



Scheme 2-1. Lewis acid catalyzed cyclopropene cycloisomerization.

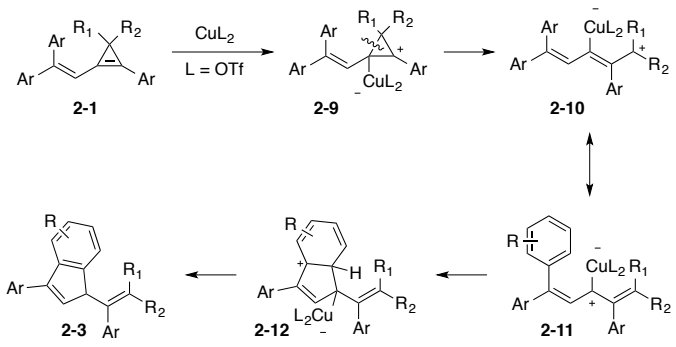
Mechanistically, it was proposed that the naphthalene formation involves the initial generation of $HBF_n(OH)_{4-n}$, a Brønsted acid, upon reaction of BF_3·OEt with trace amounts of water (Scheme 2-2). Subsequent protonation of the vinyl cyclopropene **2-1** produces a cyclopropyl cation **2-4**, which undergoes ring opening to give resonance-stabilized

intermediate **2-5**. An intramolecular Friedel–Crafts reaction with the substituted aromatic ring then leads to the corresponding naphthalene **2-2** after rearomatization.



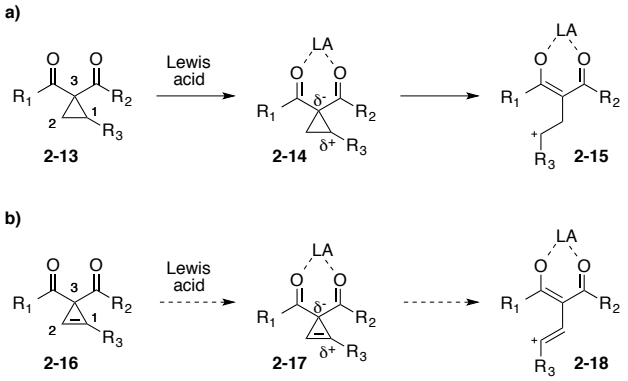
Scheme 2-2. Proposed mechanism for naphthalene formation.

In the case of indenes **2-3**, the authors proposed that due to the steric repulsion between the Lewis acid and the aromatic group, zwitterionic intermediate **2-9** is formed upon π-attack on the Lewis acid (Scheme 2-3). Subsequent ring opening provides cation-delocalized intermediates **2-10** and **2-11**. Finally, Friedel–Crafts trapping of the cation by one of the aryl rings gives the corresponding indene **3** upon rearomatization.



Scheme 2-3. Proposed mechanism for indene formation.

Due to the versatility of this small-strained ring, we were interested in examining the intramolecular cycloisomerization of the cyclopropene-3,3-dicarbonyl compounds in the presence of Lewis acids. We hypothesized an activation mode analogous to cyclopropanes **2-13**, where they have been shown to behave as 'masked' 1,3-dipoles and homo-Michael acceptors **2-15** (Scheme 2-4a).[7] In this scenario, we envisioned that the presence of electron-accepting groups at the C_3 position and a good electron-donating group at C_1 is pivotal in order to polarize the C_1-C_3 bond upon formation of a six-membered chelate **2-17** between the 1,3-dicarbonyl and the Lewis acid. This combination of electron-accepting and electron-donating groups make the C_1-C_3 bond weaker, allowing the cyclopropene to undergo a S_N1-like ring opening of the cyclopropene under mild conditions, hence requiring a lower loading of the Lewis acid. In the extreme case, this polarization would lead to bond cleavage and formation of the 1,3-dipolar vinylic cation intermediate **2-18** (Scheme 2-4b). **This is the first example of Lewis acid-catalyzed ring-opening cycloisomerization of cyclopropene-3,3-dicarbonyl compounds to give a wide array of benzo-fused heteroaromatics and heterobiaryls.**[5,8]

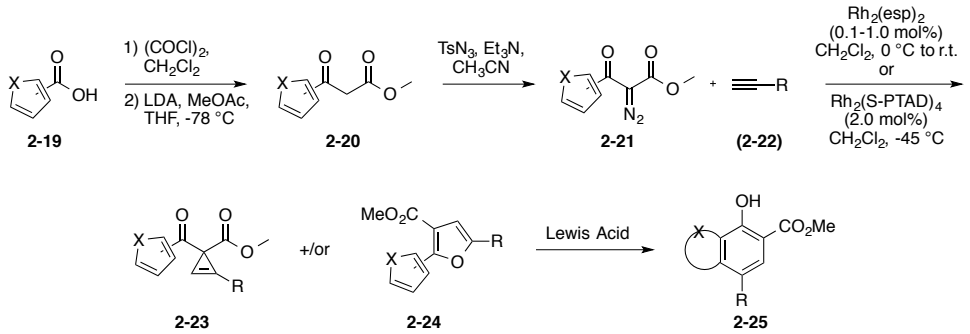


Scheme 2-4. Heterolysis of cyclopropanes 2-13 and cyclopropenes 2-16.

2.2 Results and Discussion

2.2.1 Synthetic methods

To prove our hypothesis, cyclopropene-3,3-dicarbonyl compounds were prepared taking advantage of either Gonzales-Bobes'[9] or Davies[10] Rh(II)-catalyzed cyclopropenation method using α-diazo-β-ketoesters **2-21** and terminal alkynes **2-22**. Depending on the nature of the alkyne and choice of Rh catalyst,[11] cyclopropenes **2-23** and/or furans **2-24** can be obtained from cyclopropenation reactions (Scheme 2-5). Thus, an increase of the reaction temperature with active rhodium present can lead to the rearrangement of cyclopropene **2-23** to furan **2-24**. Also, it is important to note that under the same Lewis acid-catalyzed reaction conditions, cyclopropenes **2-23** and furans **2-24** readily undergo ring-opening cycloisomerization to form the benzo-fused heteroaromatics **2-25**. The focus of this Chapter is the cycloisomerizations of the cyclopropene-3,3-dicarbonyl compounds; thus, furan ring-opening cycloisomerizations will not be discussed in details. However, the scope of the furan cycloisomerizations will be summarized in this Chapter.

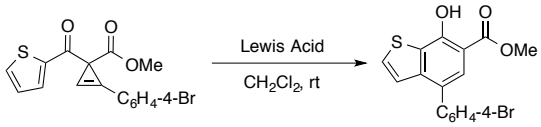


Scheme 2-5. Synthesis of cyclopropenes 2-23, furans 2-24 and their Lewis acid-catalyzed cycloisomerizations to benzo-fused heteroaromatics (2-25).

2.2.2 Reaction optimization

To optimize the reaction conditions, we chose to utilize the cyclopropene-3,3-dicarbonyl compound **2-23a**, derived from 2-thiophene, as the model substrate. Inspired by our previous report,[7b] we treated **2-23a** with 30 mol% $In(OTf)_3$ in CH_2Cl_2 at room temperature (Table 2-1). The reaction went to full conversion to give the desired benzo[*b*]thiophene **2-25a** after ~2 h. When other Lewis acids were explored, such as $Sc(OTf)_3$, a significant amount of furan **2-24a** was observed. $Cu(OTf)_2$ gave **2-25a** after ~10 h. Others, such as AgOTf, $Al(OTf)_3$ and $Zn(OTf)_2$, were much less efficient and did not achieve completion even after 12 h. Other solvents were screened without improvement on the reaction yield. A longer reaction time (~10 h) was observed upon reducing the catalyst loading to 5 mol%, but the product **2-25a** was obtained in 86% yield.

Table 2-1. Lewis acid screen for cycloisomerization of cyclopropenes.



2-23a **2-25a**

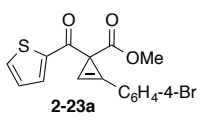
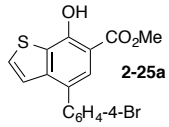
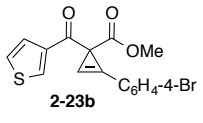
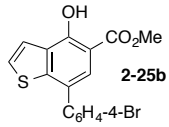
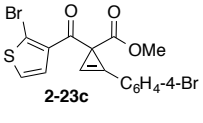
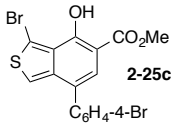
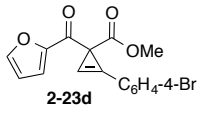
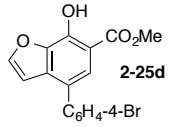
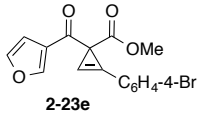
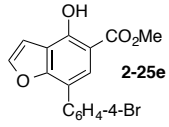
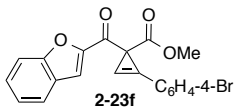
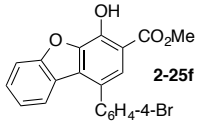
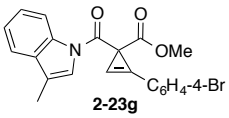
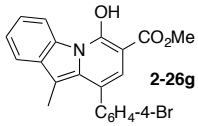
Lewis Acid (30 mol%)	Time (h)
$In(OTf)_3$	2
$Sc(OTf)_3$	3
AgOTf	>12
$Al(OTf)_3$	>12
$Zn(OTf)_2$	>12
$Cu(OTf)_2$	8

2.2.3 Reaction scope: Benzo-fused (hetero)aromatics from cyclopropene-3,3-dicarbonyl

A variety of cyclopropene-3,3-dicarbonyl compounds were synthesized and submitted to the optimized cycloisomerization conditions to yield the corresponding benzo-fused heteroaromatic compound (Tables 2-2 and 2-3).

We began our study by exploring the effect of the pendant heteroaryl group. With our model substrate **2-23a**, derived from 2-thiophene diazo **2-21a**, benzothiophene **2-25a** was obtained in 86% yield (Table 2-2, entry 1). Meanwhile, 3-thienyl cyclopropene **2-23b** underwent cycloisomerization to furnish benzothiophene **2-25b** in 48% yield (Table 2-2, entry 2). 2-Bromo-3-thiophene cyclopropene **2-23c** provided the benzo[*c*]thiophene **2-25c** in 43% (Table 2-2, entry 3). Benzofurans **2-25d** and **2-25e**, cycloisomerized from 2-furyl and 3-furyl cyclopropene **2-23d** and **2-23e**, required higher loading of $In(OTf)_3$ (30 mol%) and were formed in 26% and 46% yield, respectively (Table 2-2, entry 4 and 5). These low yields could be attributed to the degradation of the cyclopropenes in presence of the Lewis acid. Dibenzofuran **2-25f** was obtained from cyclopropene **2-23f** in 48% yield (Table 2-2, entry 6). It is important to note that the benzofuran and dibenzofuran moieties are present in a number of natural products. Interestingly, *N*-acyl-3-methylindole cyclopropene **2-23g** provided pyrido[1,2-*a*]indole **2-26g** in 65% yield (Table 2-2, entry 7). It is important to note that pyrido[1,2-*a*]indoles are found in many natural products.

Table 2-2. Cycloisomerization of cyclopropene-3,3-dicarbonyls.

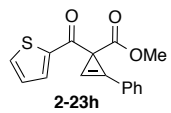
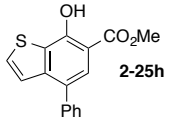
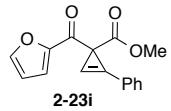
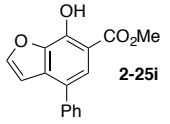
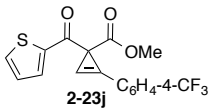
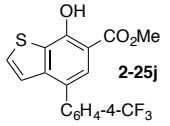
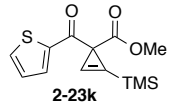
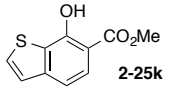
Entry	Cyclopropene	Product	Yield (%)[d]
1	 **2-23a**	 **2-25a**	86
2[a]	 **2-23b**	 **2-25b**	48
3	 **2-23c**	 **2-25c**	43[c]
4[a]	 **2-23d**	 **2-25d**	26
5[a]	 **2-23e**	 **2-25e**	46
6	 **2-23f**	 **2-25f**	65
7[b]	 **2-23g**	 **2-26g**	62

a) Performed with 30 mol% in(OTf)$_3$, *b*) performed with 30 mol% In(OTf)$_3$ at 40 °C, *c*) mixture of mono- and dibrominated products determined by MS, *d*) isolated yields

Next, we synthesized cyclopropenes with different groups at C_1. As expected, cyclopropenes substituted with a phenyl group (**2-23h** and **2-23i**), provided their corresponding benzothiophene **2-25h** and benzofuran **2-25i** in 63 and 46% yield, respectively (Table 2-3, entries 1 and 2). When a cyclopropene with highly electron-withdrawing group, such as C_6H_4-4-CF_3 (**2-23j**), as anticipated, no cycloisomerized product was obtained (Table 2-3, entry 3). This is due to the fact that this group does not stabilize the build-up of positive

charge at C_1. It is notable that when we subjected a TMS-substituted cyclopropene (**2-23k**), derived readily from TMS-acetylene, to our cycloisomerization reaction conditions, only the unsubstituted product was isolated (**2-25k**, Table 2-3, entry 4). This can be rationalized by the fact that upon the formation of the six-membered chelate, the cycloisomerization undergoes with an inverse regioselectivity, followed by a protiodesilylation to furnish our unsubstituted product.

Table 2-3. Effect on the C_1 substitution for the cyclopropene cycloisomerization.

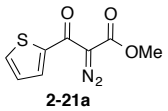
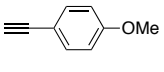
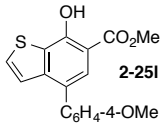
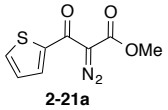
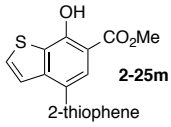
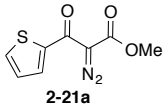
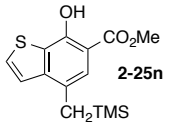
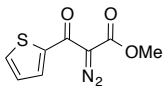
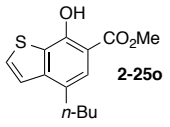
Entry	Cyclopropene	Product	Yield (%)[a]
1	 **2-23h**	 **2-25h**	63
2	 **2-23i**	 **2-25i**	46
3	 **2-23j**	 **2-25j**	NR[b]
4	 **2-23k**	 **2-25k**	58

a) Isolated yields, *b*) no reaction

In some cases, the isolation of highly reactive cyclopropenes was not possible due to either decomposition or isomerization to the corresponding furan substrate. For these cases we decided to implement a tandem cyclopropenation/cycloisomerizations protocol. Starting from the diazo compound **2-21a** and 4-ethynylanisole **2-22l**, benzothiophene **2-25l** was obtained in only 15% yield (Table 2-4, entry 1). Similarly, benzothiophenes **2-25m** and **2-25n** were obtained in 25 and 30% yield, respectively, from their corresponding alkynes **2-**

22m and **2-22n** (Table 2-4, entries 2 and 3). These low yields could be attributed to different factors such as rapid decomposition of the diazo or the decomposition of the highly reactive cyclopropene under Lewis acid conditions. For cyclopropene **2-23n** (not isolated), besides bearing an alkyl group, the cycloisomerization is possible due to the stabilization of the build-up of positive charge at C_1 by the β-silyl effect. In contrast, for cyclopropene **2-23o** (not isolated), was found that a simple alkyl group, such as *n*-butyl, is not donating enough to promote the reaction (Table 2-4, entry 4). Besides the low yield or no reactivity of these substrates, these results provide some useful mechanistic insights.

Table 2-4. Tandem cyclopropenation/cycloisomerization protocol.

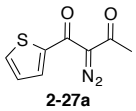
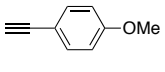
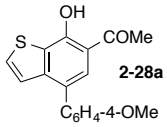
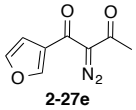
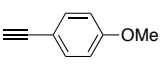
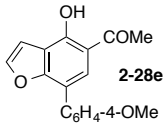
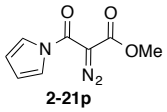
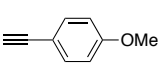
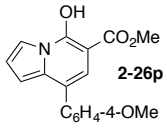
Entry	Diazo	Alkyne	Product	Yield (%)[a]
1	 **2-21a**	 **2-22l**	 **2-25l** C_6H_4-4-OMe	15
2	 **2-21a**	 **2-22m**	 **2-25m** 2-thiophene	25
3	 **2-21a**	 **2-22n**	 **2-25n** CH_2TMS	30
4	 **2-21a**	 **2-22o**	 **2-25o** *n*-Bu	NR[b]

a) Isolated yield, *b*) no reaction

Finally, after fully examining both the heteroaryl effect and the substituent effect, we then changed directions and focused on the difference of the acceptor groups. Having a ketone as an acceptor group will provide another chemical handle such as alkylation or condensations post-cycloisomerization. Taking diazo **2-27a** with a ketone as the acceptor

group and subjecting it to 4-ethynylanisole **2-22l**, we found that only the benzofused heteroaromatic product **2-28a** was isolated in modest yield of 62% (Table 2-5, entry 1). We also wanted to apply this for the formation of benzofurans, and we found that subjecting diazo **2-27e**, derived from 3-furan, benzofuran **2-28e** was formed in 31% yield (Table 2-5, entry 2). Changing the acceptor group to an amide, such as the case of *N*-acylpyrrole diazo **2-21p**, we were able to form indolizine **2-26p** in 51% yield (Table 2-5, entry 3). This strategy allows for us to quickly access substituted benzofused heteroaromatic products in modest yield and short reaction times.

Table 2-5. Effects of varying the acceptor.

Entry	Diazo	Alkyne	Product	Yield (%)[a]
1	 **2-27a**	 **2-22l**	 **2-28a** C_6H_4-4-OMe	62
2	 **2-27e**	 **2-22l**	 **2-28e** C_6H_4-4-OMe	31
3	 **2-21p**	 **2-22l**	 **2-26p** C_6H_4-4-OMe	51

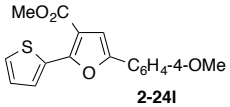
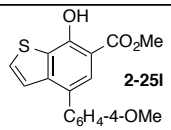
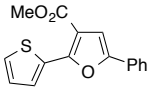
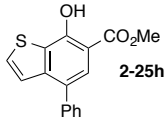
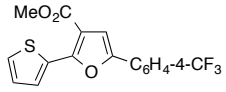
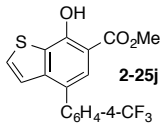
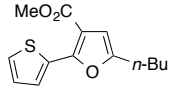
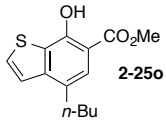
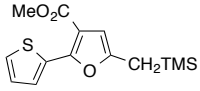
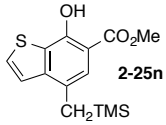
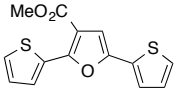
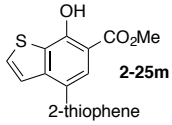
a) Isolated yield

2.2.4 Reaction scope: Benzo-fused (hetero)aromatics from furan substrates

The cycloisomerizations of furans were conducted as detailed for cyclopropenes. Furans bearing an electron-donating group underwent cycloisomerizations under Lewis acid conditions in moderate to good yields (55-86% yield) to provide us with an array of benzo-fused compounds (Tables 2-6 and 2-7). As expected, furans containing an electron poor aromatic group or a simple alkyl group did not undergo cycloisomerization. This furan

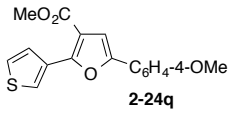
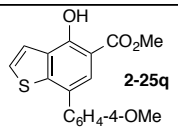
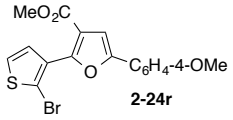
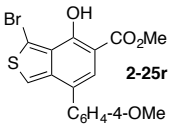
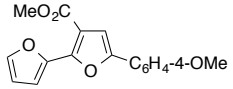
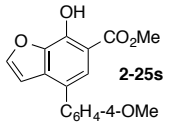
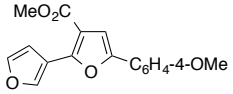
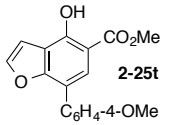
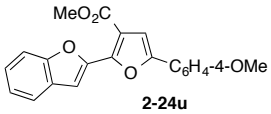
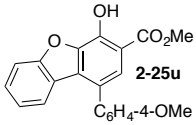
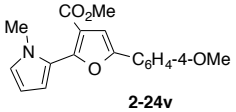
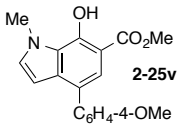
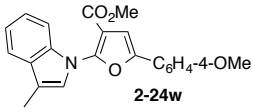
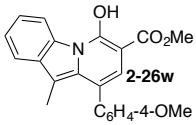
cycloisomerization still needs to be explored in more details, not only for sharing the same proposed reaction intermediate (1,3-dipolar vinylic cation intermediate **2-18**) but because more substituted furan substrates can be accesed through other synthetic methods, allowing more diversity on the benzo-fused heteroaromatics that can be formed.

Table 2-6. Cycloisomerization of furans to benzo-fused heteroaromatic compounds.

Entry	Furan	Product	Yield (%)[b]
1	 **2-24l**	 **2-25l**	86
2	 **2-24h**	 **2-25h**	86
3	 **2-24j**	 **2-25j**	NR[c]
4	 **2-24o**	 **2-25o**	NR[c]
5[a]	 **2-24n**	 **2-25n**	68
6	 **2-24m**	 **2-25m**	83

a) Performed with 1,2-DCE at reflux, *b*) isolated yield, *c*) no reaction

Table 2-7. Cycloisomerization of various heteroaryl furans to benzo-fused heteroaromatics.

Entry	Furan	Product	Yield (%)[b]
1	 **2-24q**	 **2-25q**	82
2	 **2-24r**	 **2-25r**	55
3[a]	 **2-24s**	 **2-25s**	78
4	 **2-24t**	 **2-25t**	82
5	 **2-24u**	 **2-25u**	69
6	 **2-24v**	 **2-25v**	78
7	 **2-24w**	 **2-26w**	69

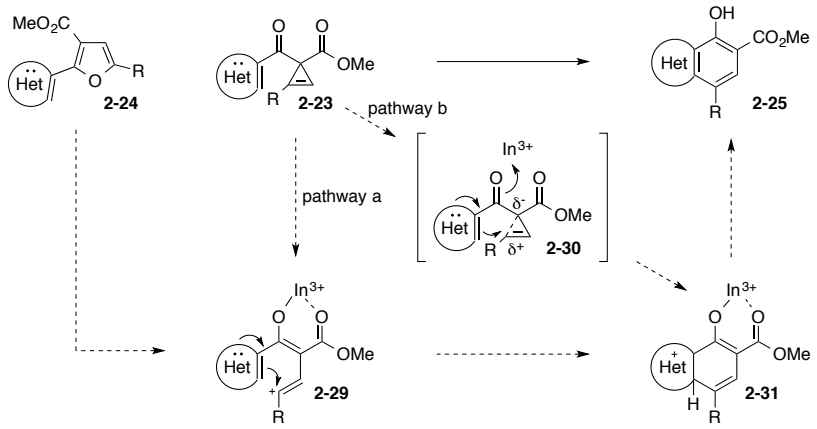
a) Performed with 1,2-DCE at reflux, *b*) isolated yield

2.2.5 Mechanistic rationale

We envision that two plausible reaction pathways may occur depending on the extent of C_1-C_3 bond polarization (Scheme 2-6). Complete heterolytic cleavage (pathway a) would afford the intermediate vinylic cationic species **2-29**, which should undergo a Friedel–Crafts-type alkenylation to give **2-31**. Alternatively, a direct nucleophilic (S_N1-like) ring-opening mechanism (pathway b) could be responsible for the product formation. Given that electron-poor aromatics and simple alkyl groups (such as *n*-butyl) do not work, we believe that pathway a is more plausible due the importance of the substituent in stabilizing the vinylic

carbocation. Reaction enthalpies of substituted vinylic cations have established that simple alkyl and electron-poor aromatics result in a large-degree destabilization.[12] Therefore, through pathway a, these substrates are predicted to be unreactive. However, the two pathways can seemingly converge if the intermediate **2-29** is substantially short-lived prior to the Friedel–Crafts reaction.

Another mechanism insight comes from the isomerization of furan substrates **2-24**. The fact that furans need to go through a ring-opening followed by enol isomerization to afford the benzo-fused compound **2-25**, its indicative of a short living stabilized vinylic carbocation **2-29**. This type of ring-opening mechanism has never seen before for cyclopropenes.



Scheme 2-6. Proposed pathways for the isomerization mechanism.

2.3 Conclusion

Through the cycloisomerization of cyclopropene-3,3-carbonyl compounds we were able to show a different mode of action never seen before for cyclopropenes. We believe this is due to the strategic positioning of acceptor and donor groups on the cyclopropene. The

existence of a short-living 1,3-dipolar vinylic cation intermediate was proven by using furans to access benzo-fused heteroaromatics. A wide array of highly substituted benzannulated products, such as benzofurans, dibenzofurans, benzothiophenes and indoles alkaloids, were formed in up to 86% yield from furan and cyclopropene cycloisomerizations using low Lewis acid loading. However, the furan transformation needs to be studied in more details in order to form multi-substituted heteroaromatic compounds that cannot be accessed via the cyclopropene cycloisomerization.

2.4 Experimental

The experimental data and compounds characterization has been published and can be found on the cited reference.[8]

2.5 References

1. For recent reviews on the reactivity of cyclopropenes, see: Miege, F.; Meyer, C.; Cossy, J.; *Beilstein J. Org. Chem.* **2011**, *7*, 717-734; b) Rubin, M.; Rubina, M.; Gevorgyan, V.; *Chem. Rev.* **2007**, *107*, 3117-3179; c) Zhu, Z.-B.; Wei, Y.; Shi, M. *Chem. Soc. Rev.* **2011**, *40*, 5534-5563.
2. For examples of the rearrangement of cyclopropenes into furans, see: a) Chen, J.; Ma, S. *Chem. Asian J.* **2010**, *5*, 2415-2421; b) Chen, J.; Ni, S.; Ma, S. *Synlett* **2011**, 931-934; c) Ma, S.; Zhang, J. *J. Am. Chem. Soc.* **2003**, *125*, 12386-12387; d) Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1997**, *62*, 1642-1652; e) Tomilov, Y. V.; Shapiro, E. A.; Protopopova, M. N.; Ioffe, A. I.; Dolgii, I. E.; Nefedov, O. M.; *Izv. Akad. Nauk SSSR Ser. Khim.* **1985**, 631-639; f) Davies, H. M. L.; Romines, K. R.

Tetrahedron **1988**, *44*, 3343-3348; g) Pirrung, M. C.; Blume, F. *J. Org. Chem.* **1999**, *64*, 3642-3649.

3. Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem.* **2007**, *119*, 4841-4843; *Angew. Chem. Int. Ed.* **2007**, *46*, 4757-4759.
4. Chuprakov, S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 4463-4466.
5. Phun, L.; Aponte-Guzmán, J.; France, S. *Synlett* **2012**, *23*, 2723.
6. Shao, L.-X.; Zhang, Y.-P.; Qi, M.-H.; Shi, M. *Org. Lett.* **2007**, 9, 117.
7. a) Cavitt, M. C.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804; b) Phun, L. H.; Patil, D. V.; Cavitt, M. A. *Org. Lett*. **2011**, *13*, 1952.
8. Phun, L. H.; Aponte-Guzman, J.; France, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3198.
9. González-Bobes, F.; Fenster, M. D. B.; Kiau, S.; Kolla, L.; Kolotuchin, S.; Soumeillant, M. *Adv. Synth. Catal.* **2008**, *350*, 813.
10. Briones, J. F.; Davies, H. M. *Tetrahedron* **2011**, *67*, 4313.
11. The cyclopropenation reaction is under kinetic control. The cyclopropene represents the kinetic product while the furan represents the thermodynamic product. Depending on the substrate and which Rh(II) catalyst is used the ratio of the two products varies.
12. vanAlem, K.; Lodder, G.; Zuilhof, H. *J. Phys. Chem. A* **2002**, *106*, 10681-10690.
13. Patil, D. V.; Phun L. H.; France, S. *Org. Lett.* **2010**, *12*, 5684.
14. Patil, D. V.; Cavitt, M. A.; Gryzbowski, P.; France, S. *Chem. Commun*. **2011**, *47*, 10278.
15. Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, 7198.
16. Hachtel, S.; Dedio,J.; Pernerstorfer, J.; Shimshock, S.; Lanter, C.; Kosley, R. Preparation of fused bicycliccarboxamide derivatives, particularly 5,6,7,8-

tetrahydronaphthalene carboxamides and benzothiophenecarboxamides, as inhibitors of CXCR2 for treatment of chemokine-mediated diseases. Patent 2008000408, Jan 03, 2008.

CHAPTER 3

BENZANNULATION VIA ALKYLIDENE CYCLOPROPANE-1,1-KETOESTERS FORMAL HOMO-NAZAROV-TYPE CYCLIZATIONS

The work about to be presented is adapted from a previous publication. My contribution on this project includes the synthesis and characterization for all the compounds reported. For a better understanding on the topic, access the corresponding reference.[6]

3.1 Introduction

Alkylidene cyclopropanes (ACPs) have been considerably studied for the past fifty years.[1] With 12-13 kcal mol^{-1} greater ring strain[2] than simple cyclopropanes, these small carbocycles possess a remarkable thermodynamic driving force that allows transformations that otherwise would be unfavorable. Thus, ACPs are considered useful building blocks in organic chemistry besides their presence in naturally occurring and biologically active compounds. The presence of an exocyclic double bond and a three-membered ring makes ACPs exploitable intermediates and appealing to the synthetic community. For this reason, several transformations at the double bond have been reported, including H-Nuc additions, hydrometalations, dimetalations, and cycloadditions. Also, ring-opening reactions in the presence of nucleophiles, transition metal catalysts, and acids have been of great interest.[1]

Acid-promoted ring-opening pathways are one of the most attractive transformations and are categorized into two general patterns: heterolytic cleavage of the C_1/C_3 distal bond and heterolytic breakage of the C_2/C_3 proximal bond (Figure 3-1a). By altering the substitution pattern about the cyclopropane and by choosing appropriate metal reagents or

catalysts, ring-opening selectivity can be achieved. For example, distal cleavage (C_1/C_3 cleavage) is preferentially observed when ACPs are substituted with acceptors on C_1 of the cyclopropyl ring (Figure 3-1b).

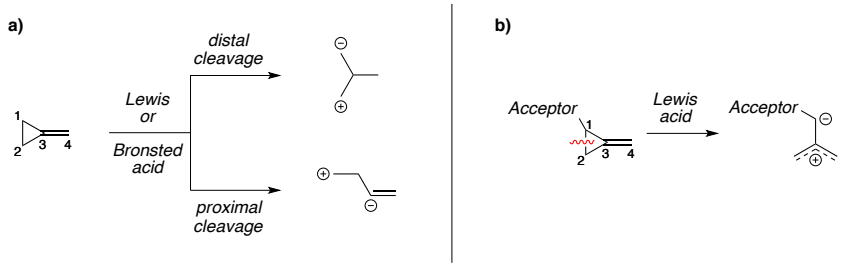
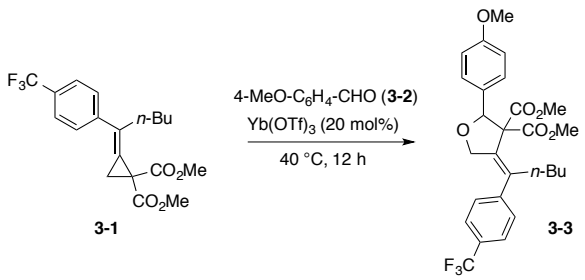
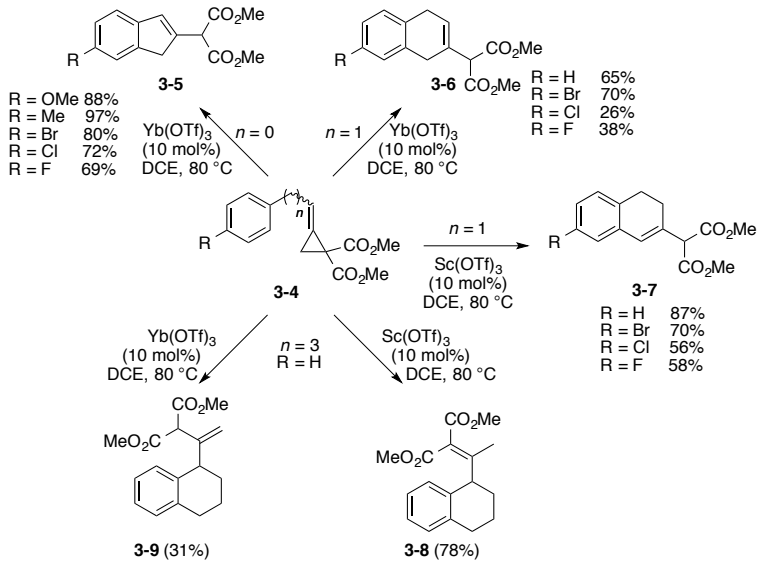


Figure 3-1. Heterolytic reactivity of alkylidene cyclopropanes (ACPs) [adapted from manuscript][6].

A special attention has been paid to ACPs bearing two electron-withdrawing groups (EWG) on C_1. Coordination of the acceptor groups with a Lewis acid induces a distal bond ring-opening to give a resonance stabilized 1,3-dipole that can reacts with a nucleophile inter- or intramolecularly. As an example, the intermolecular trapping of the carbocation was shown in the synthesis of tetrahydrofuran **3-3** from ACP **3-1** and *p*-anisaldehyde **3-2** (Scheme 3-1).[3] In contrast, different annulated scaffolds can be access from an intramolecular Friedel-Crafts-type alkylation as shown by Wang and co-workers. This first intramolecular Friedel-Crafts-type alkylation of ACP-1,1-diesters **3-4** initiated with a distal cleavage and ended with the synthesis of indenes **3-5** and di- tetrahydronaphthalene derivatives **3-6** to **3-9** (Scheme 3-2).[4]



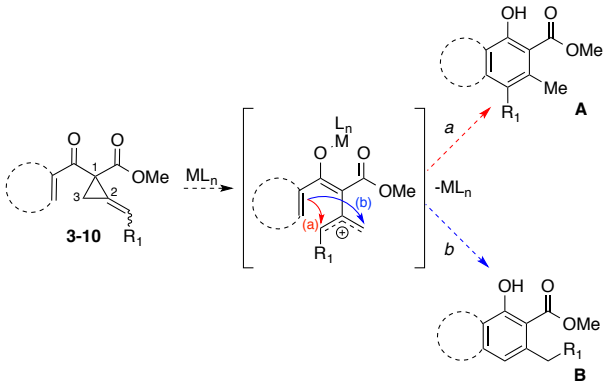
Scheme 3-1. Intermolecular reactivity of ACP-1,1-diesters with an aldehyde.



Scheme 3-2. Intramolecular reactivity of ACP-1,1-diesters with Lewis acids.

Despite the progress with ACPs over the past years,[1] the intramolecular Friedel-Crafts-type alkylation of ACPs still underexplored. In a seminal report, Shi and co-workers reported the synthesis of naphthalene derivatives from ACP diaryl alcohols.[5] However, no benzannulation reaction has been demonstrated, besides our report, using ACP-1,1-diesters.[6] For this reason, we sought to explore the compatibility of ACP-1,1-dicarbonyls within our mechanistic regime.[7] Here, we disclose the catalytic, formal homo-Nazarov-type intramolecular ring-opening cyclizations of ACP-1,1-ketoesters in order to access several

benzannulated molecules (Scheme 3-3). Mechanistically, the reaction involves Lewis acid-catalyzed heterolytic distal cleavage of the ACP **3-10** to afford a 1,3-dipole containing a resonance stabilized allyl cation. Intramolecular π-attack can occur at either end of the delocalized allyl cation (pathways a and b) to afford a six-membered ring. Proton loss and alkene isomerization provide two isomeric *o*-phenolic ester[8] derivatives **A** and **B**, whose ratios are dependent upon the nature of R_1. In most cases, product **A**, arising from the thermodynamically preferred allyl cation, is expected to be the major product formed.



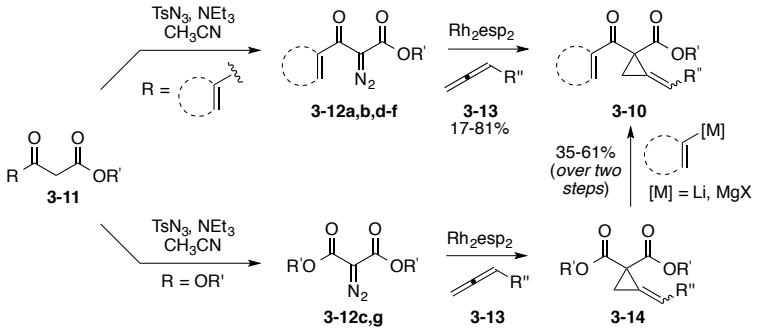
Scheme 3-3. Formal Homo-Nazarov-Type Cyclizations of ACPs (adapted from manuscript)[6].

3.2 Results and Discussion

3.2.1 Synthetic methods

Several procedures for the synthesis of ACPs, such as rearrangements, base-promoted eliminations from 1-alkyl-1-halo-substituted cyclopropanes, metal-mediated formations, between others, has been disclosed.[1a,9] However, the addition of carbenes to allenes is the most straightforward approach to ACPs and has found wide applications since its first description in the early 1960s.[10] For our purpose, ACPs **3-10** were prepared in one of two

ways using the Rh(II)-catalyzed cyclopropanation of allenes **3-13** with α-diazo dicarbonyl compounds **3-12** (Scheme 3-4).[11]



Scheme 3-4. Preparation of ACP-1,1-ketoesters (adapted from manuscript)[6].

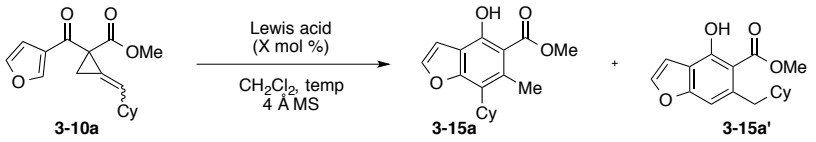
3.2.2 Reaction optimization

Due to the commercial availability of cyclohexyl allene **3-13a** and the large amount of the corresponding α-diazo compound on hand, 3-furyl ACP **3-10a** was chosen as the model system for reaction optimization. Various metal triflates were examined at 15 mol% in CH_2Cl_2 (Table 3-1). For ACP **3-10a**, the reactions proved to be regioselective for the favored benzofuran **3-15a** (>88:12 in all cases). For $In(OTf)_3$, $Sc(OTf)_3$, $Al(OTf)_3$, and $Ga(OTf)_3$, each reaction went to completion and afforded **3-15a** in 66−74% yield (Table 3-1, entries 1-4). In contrast, $Cu(OTf)_2$ and $Zn(OTf)_2$ proved to be inefficient catalysts for the trans-formation as low yields/conversions (<20%) of **3-15a** were obtained (Table 3-1, entries 5 and 6).

Interestingly, although the reaction with $Yb(OTf)_3$ did not reach completion,[12] benzofuran **3-15a** was obtained in 57% yield along with ~40% unreacted starting material (Table 3-1, entry 7). When heating to reflux, the reaction went to completion in ~12 h and

the product yield increased to 91% (Table 1, entry 8). Similar yield improvements were obtained for the other Lewis acids in CH_2Cl_2 at reflux (Table 3-1, entries 9-12); however, none of the catalysts gave higher yields than $Yb(OTf)_3$. When the $Yb(OTf)_3$ loading was changed to either 20 and 10 mol%, the yields decreased to 74% and 81%, respectively (Table 3-1, entries 13 and 14).[13] Therefore, 15 mol% $Yb(OTf)_3$ in CH_2Cl_2 at reflux was chosen as the conditions for the examination of substrate scope.[14]

Table 3-1. Optimization for the benzannulation of ACP-1,1-ketoesters (adapted from manuscript)[6].



Entry[a]	Lewis acid	Loading (mol %)	Temp (°C)	Time (h)	% Yield[b]	3-15a:3-15a'[c]
1	$In(OTf)_3$	15	rt	8	66	98:2
2	$Sc(OTf)_3$	15	rt	8	68	98:2
3	$Al(OTf)_3$	15	rt	20	74	98:2
4	$Ga(OTf)_3$	15	rt	9	70	99:1
5	$Cu(OTf)_2$	15	rt	48	20	99:1
6	$Zn(OTf)_2$	15	rt	48	--d	99:1
7	$Yb(OTf)_3$	15	rt	19	57	98:2
8	**$Yb(OTf)_3$**	**15**	**40**	**12**	**91**	**95:5**
9	$In(OTf)_3$	15	40	4	77	99:1
10	$Sc(OTf)_3$	15	40	4	74	99:1
11	$Al(OTf)_3$	15	40	8	80	99:1
12	$Ga(OTf)_3$	15	40	4	77	99:1
13	$Yb(OTf)_3$	20	40	10	74	97:3
14	$Yb(OTf)_3$	10	40	14	81	97:3

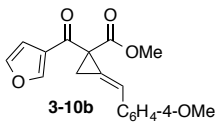
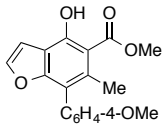
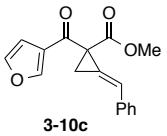
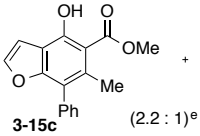
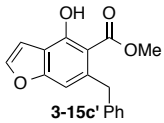
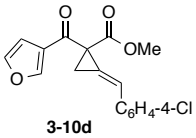
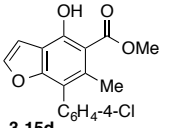
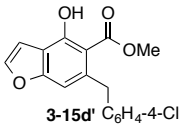
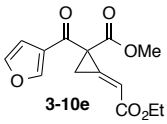
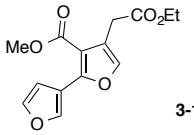
a) Reactions run with Lewis acid, ACP **3-10a**, and 4 Å molecular sieves in CH_2Cl_2 (0.1 M) at the indicated temperature; b) Combined yield of **3-15a** and **3-15a'** after column chromatography; c) Product ratios determined by ^1H NMR of isolated mixture; d) ~15% conversion observed as determined by crude ^1H NMR.

3.2.3 Reaction scope

First, the effects of the alkylidene substituents were examined (Table 3-2). When the alkylidene was substituted with a 4-methoxyphenyl group (as in **3-10b**), the expected benzofuran **3-15b** was formed in 53% as the only product (Table 3-2, entry 1). In contrast, when the substituent is phenyl (as in **3-10c**), a 2.2:1 mixture of **3-15c** and its isomer **3-15c′**

was obtained in 71% combined yield (Table 3-2, entry 2). A similar result was observed with ACP **3-10d** (bearing a 4-chlorophenyl group) as a 53% yield of a 2.0:1 mixture of **3-15d**:**3-15d′** was formed (Table 3-2, entry 3). These observations suggest activation barriers that are closer in energy for the intramolecular cyclization at either terminus of the allyl cation as compared to ACP **3-10b**.[15]

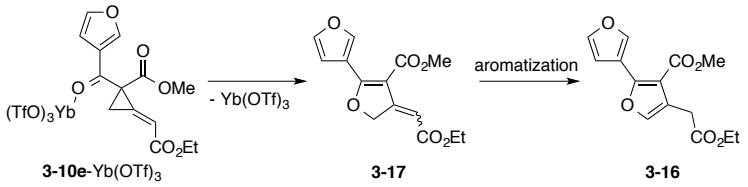
Table 3-2. Alkylidene substituent effect (adapted from manuscript)[6].

Entry[a]	Substrate	Product(s)	% Yield[b]
1	 **3-10b**	 **3-15b**	53%
2	 **3-10c**	 **3-15c** (2.2 : 1)[e]  **3-15c'**	71%[c]
3	 **3-10d**	 **3-15d** (2.0 : 1)[e]  **3-15d'**	53%[c,d]
4	 **3-10e**	 **3-16**	69%

a) Reactions run with Lewis acid (15 mol%), ACP **3-10**, and 4 Å molecular sieves in CH_2Cl_2 (0.1 M) at 40 °C; b) Isolated yield after column chromatography; c) Combined isolated yield of **3-15** and **3-15'**; d) Reactions performed in 1,2-dichloroethane at reflux; e) Product ratios determined by ^{1}H NMR of isolated mixture.

When the alkylidene substituent was an electron-withdrawing group, an alternative reaction outcome was observed. For instance, when the alkylidene substituent was an ester group, the 2,3′-bifuran derivative **3-16** was generated in 69% yield and none of the benzofuran product(s) were seen (Table 3-2, entry 4).[16] Bifuran **3-16** arises from an intramolecular attack of the enolate oxygen on the alkylidene cyclopropane to form a transient dihydrofuran intermediate that undergoes aromatization to the furan (Scheme 3-5).

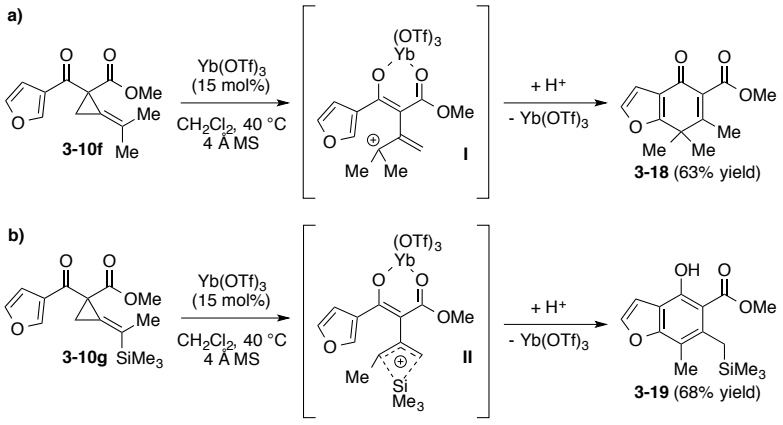
The regiochemical outcome suggests that the allyl cation is not formed, which is in agreement with the destabilizing effect of an electron-withdrawing substituent on an allyl cation.



3-10e-Yb(OTf)$_3$ **3-17** **3-16**

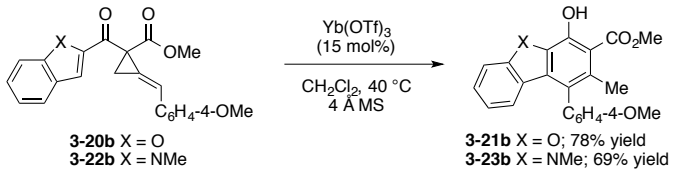
Scheme 3-5. Formation of 2,3′-bifuran 3-16 (adapted from manuscript)[6].

In hopes of generating more functionalized/functionalizable products, ACPs bearing a second substituent on the alkylidene were employed (Scheme 3-6). In one example, the ACP (**3-10f**) had two methyl alkylidene substituents and gave the 4-oxo-4,7- dihydrobenzofuran derivative **3-18** in 63% yield (Scheme 3-6a). Compound **3-18** contains both a quaternary center and an alkylidene β-ketoester moiety, which can serve as a site for further reactivity.[17] In another example, the alkylidene was substituted with a methyl and a trimethylsilyl group (Scheme 3-6b). Benzofuran **3-19** was formed in 68% yield and presumably arises via formation of a silyl-stabilized[18] methyl allyl cation **II** followed by Friedel−Crafts-type cyclization and subsequent aromatization. This approach offers potential for functionalization, as the proper choice of silyl group would allow for facile C−C[19] and C−O[20] bond formation.



Scheme 3-6. Effects of alkylidene disubstitution (adapted from manuscript)[6].

To further explore the reaction scope, the reactive π-systems on the ACP were modified in three different ways and the resulting reactivities were cataloged. First, other heteroaryl π-systems were employed under the same reaction conditions (Scheme 3-7).[7a,21] The 2-benzofuryl ACP **3-20b** bearing an 4-methoxyphenyl alkylidene substituent gave the corresponding dibenzofuran product **3-21b** in 78% yield. Similarly, 2-indolyl ACP **3-22b** smoothly afforded carbazole **3-23b** in 69% yield.

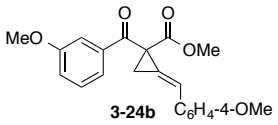
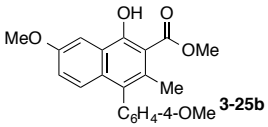
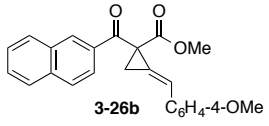
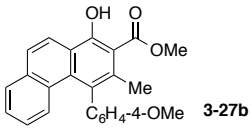
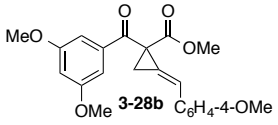
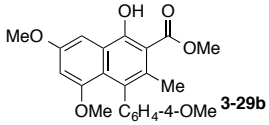
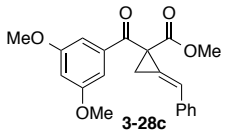
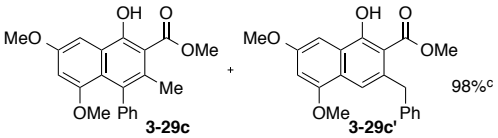
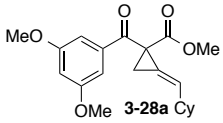
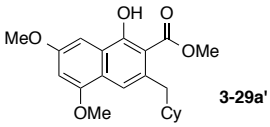


Scheme 3-7. Formation of dibenzofuran 3-21b and carbazole 3-23b (adapted from manuscript)[6].

Next, the effect of employing aryl groups[22] as the intramolecular π-nucleophile for the ring-opening cyclization was examined (Table 3-3). When the ACP was substituted with a 3-methoxyphenyl group as the π-donor and a 4-methoxyphenyl group on the alkylidene (as in **3-24b**), the expected regioisomeric naphthalene product **3-25b** was formed in 77% yield

(Table 3-3, entry 1). If the π-nucleophile is a 2-naphthyl group, two regioisomeric products are possible via Friedel−Crafts-type alkylation at C_1 or C_3 of the naphthalene. The preferred reactivity is expected to occur at C_1 given the relative stability of the resulting Wheland intermediate.[23] Indeed, the only observed cyclization product is phenanthrene **3-27b**, resulting from C_1 attack, in 44% yield (Table 3-3, entry 2). When 3,5-dimethoxyphenyl was the π-donor, regiochemical outcomes were found to be dependent upon the alkylidene substituent. For instance, a 4-methoxyphenyl substituent gives the favored naphthalene product **3-29b** in 80% yield (Table 3-3, entry 3), whereas a phenyl group gives a 1.8:1 preference for the less energetically favorable **3-29c′** over **3-29c** (98% yield, Table 3-3, entry 4). This outcome is seemingly the result of a combination of electronic and steric effects in the transition state for cyclization. To assess the steric influence on the regiooutcome, ACP **3-28a** (bearing the cyclohexyl alkylidene substituent) was prepared. As anticipated, the only observed product was naphthalene derivative **3-29a′** in 39% yield (Table 3-3, entry 5). Thus, sterics directly influences the cyclization pathways and product outcomes.

Table 3-3. Aryl groups as the intramolecular π-nucleophiles (adapted from manuscript)[6].

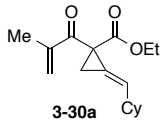
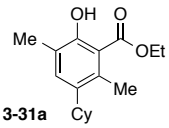
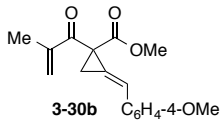
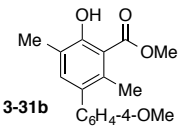
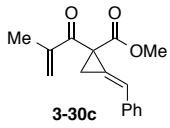
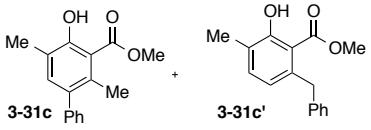
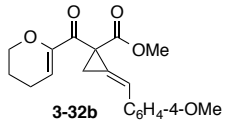
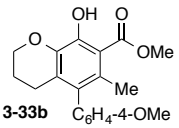
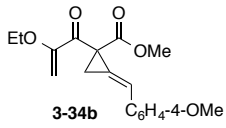
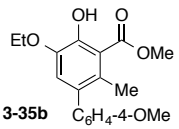
Entry[a]	Substrate	Product(s)	% Yield[b]
1	 **3-24b**	 **3-25b**	77%
2	 **3-26b**	 **3-27b**	44%
3	 **3-28b**	 **3-29b**	80%
4	 **3-28c**	 **3-29c** + **3-29c'** (1 : 1.8)[d]	98%[c]
5	 **3-28a**	 **3-29a'**	39%[e]

a) Reactions run with Lewis acid (15 mol%), ACP (**3-24b**, **3-26b**, or **3-28a** to **3-28c**), and 4 Å molecular sieves in CH_2Cl_2 (0.1 M) at 40 °C; b) Isolated yield after column chromatography; c) Combined isolated yield of **3-29c** and **3-29c'**; d) Product ratios determined by ^{1}H NMR of isolated mixture; e) Reactions performed in 1,2-dichloroethane at reflux.

Next, the ACP π-nucleophilic moiety was changed to alkenyl groups and evaluated for performance (Table 3-4).[7a,21a,24] For the isopropenyl π-donor, similar reactivity trends were observed for ACPs bearing either a cyclohexyl (**3-30a**)[25] or a 4-methoxyphenyl (**3-30b**) alkylidene substituent, as phenols **3-31a** and **3-31b** were formed in 66% and 49% yield, respectively (Table 3-4, entries 1 and 2). For **3-30c**, bearing the phenyl group, an unsurprising 2.7:1 mixture of phenols **3-31c** and **3-31c′** was observed in 59% yield (Table 3-4, entry 3). With dihydropyran as the π-nucleophile, phenol **3-33b** was obtained in 26% yield (Table 3-4, entry 4). The conformation and steric impact of the pyranyl ring are implicated in the decreased reaction efficiency. To examine that premise, the ACP **3-34b**, containing an ethoxy vinyl subtituent, was prepared. Compound **3-34b**, having less destabilizing steric and

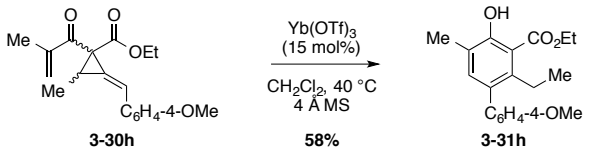
conformational influences, should perform more effectively. Indeed, **3-34b** smoothly afforded phenol **3-35b** in 51% yield (Table 3-4, entry 5).

Table 3-4. Performance of alkenyl ketone substituents (adapted from manuscript)[6].

Entry[a]	Substrate	Product(s)	% Yield[b]
1	 **3-30a**	 **3-31a**	66%[c]
2	 **3-30b**	 **3-31b**	49%
3	 **3-30c**	 **3-31c** **3-31c'** (2.7 : 1.)[f]	59%[d,e]
4	 **3-32b**	 **3-33b**	26%[d]
5	 **3-34b**	 **3-35b**	51%[d]

a) Reactions run with Lewis acid (15 mol%), ACP (**3-30a** to **3-30c**, **3-32b**, or **3-34b**), and 4 Å molecular sieves in CH_2Cl_2 (0.1 M) at 40 °C; b) Isolated yield after column chromatography; c) Reactions performed with 30 mol% $Yb(OTf)_3$; d) Reactions performed in 1,2-dichloroethane at reflux; e) Combined isolated yield of **3-31c** and **3-31c'**; f) Product ratios determined by ^1H NMR of isolated mixture.

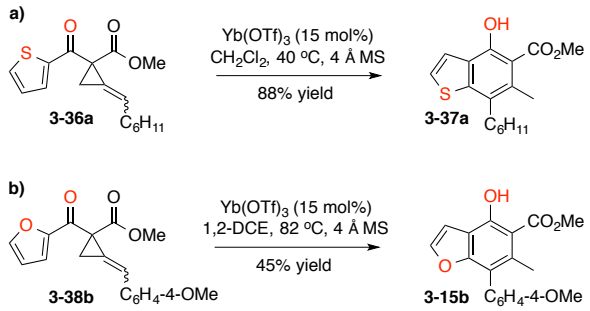
Finally, to understand the regioselectivity of the reaction of ACPs derived from 1,3-disubstituted allenes, we prepared **3-30h** from 3-methyl-1-(4-methoxyphenyl)allene **3-13h**. Under the standard reaction conditions, **3-30h** afforded the expected phenol **3-31h** in 58% yield (Scheme 3-8).



Scheme 3-8. Formation of phenol 3-31h from ACP 3-30h (adapted from manuscript)[6].

3.2.4 ACPs acyl shift

In some cases of 2-acylated heteroaryl ACPs (such as **3-36a** and **3-38b**), an acyl shift was observed to obtain benzothiophene **3-37a** and benzofuran **3-15b** in 88 and 45% yield, respectively (Scheme 3-9). This is a rare type of reactivity for ACPs that need to be further studied with computational calculations.



Scheme 3-8. Acyl shift of 2-heteroaryl ACPs.

3.3 Conclusion

We have disclosed a Lewis acid catalyzed, formal homo-Nazarov-type cyclization of alkylidene-1,1-ketoesters to form functionalized arenes and heteroarenes in up to 98% yield. Of the two possible regioisomeric outcomes, the major product arises from intramolecular π-attack on the most energetically favorable allylic cationic intermediate, unless steric constraints prevent such an attack. The choice of alkylidene substituents also affects reaction outcomes. The reaction is amenable to alkenyl, aryl and heteroaryl intramolecular π-

nucleophiles to produces a wide array of highly substituted benzofurans, dibenzofurans, naphthalenes, phenanthrenes, carbazoles, and other. This is a novel reactivity for ACP-1,1-ketoesters since no benzannulation of these substrates have been reported before.

3.4 Experimental

3.4.1 General methods

All reactions were carried out in pre-dried glassware from the oven and any additional moisture was removed by flame-drying the reaction vessel under vacuum. Each reaction proceeded under a nitrogen atmosphere with anhydrous solvents. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenone ketyl under nitrogen and stored in a Schlenk flask. 1,2-Dichloroethane and dichloromethane were purified by distillation from calcium hydride. Anhydrous acetonitrile was purchased from EMD Chemicals and used without further purification. Methyl- and ethyl acetate was fractionally distilled over P_2O_5. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification. α-Diazo compounds **3-12a** to **3-12c** and **3-12g** were synthesized as previously reported.[26] β-ketoester compounds **3-11d** to **3-11e** were synthesized as previously reported.[27] Allenes **3-13b** to **3-13d** and **3-13h** were synthesized as previously reported.[28]

Chromatographic purification was performed as flash chromatography with Dynamic Adsorbents silica gel (32-65 μm) and solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F_{254} TLC glass

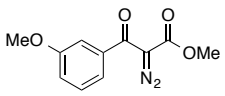
plates. Visualization was accomplished with UV light or iodine chamber. Each yield refers to an isolated, analytically-pure material.

Infrared (IR) spectra were obtained using a Bruker alpha FTIR with an ATR attachment. The IR bands are characterized as weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on Bruker 400 MHz or 500 MHz spectrometer with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a VG-70SE instrument. Uncorrected melting points were measured with a digital melting point apparatus (DigiMelt MPA 160).

3.4.2 Experimental procedures

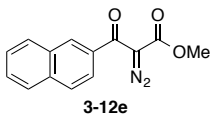
a. Formation of *α*-Diazo compounds 3-12d to 3-12f

General Diazo Transfer Procedure: To a solution of β-ketoester **3-11** (1 equiv) in CH_3CN (0.1 M) was added triethylamine (1.2 equiv) at RT. After 5 min of vigorous stirring, tosyl azide (1.2 equiv) was added and the reaction was stirred for 3 h at room temperature. At this point, the reaction mixture was concentrated *in vacuo* and purified via silica gel flash chromatography (eluting with EtOAc:Hexanes) to isolate the product.



3-12d

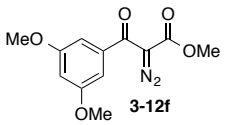
Methyl 2-diazo-3-(3-methoxyphenyl)-3-oxopropanoate (3-12d). The general procedure was followed using β-ketoester **3-11d** (10.28 g, 49.37 mmol) in CH_3CN (50.0 mL), triethylamine (5.97 g, 59.0 mmol) and tosyl azide (11.69 g, 59.3 mmol). The reaction mixture was concentrated under reduced pressure and purified via column chromatography to afford diazo **3-12d** (6.35 g, 55%) as a bright yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.30 - 7.36 (m, 1H), 7.18 - 7.22 (m, 1H), 7.15 (dd, *J* = 2.4, 1.5 Hz, 1H), 7.07 (ddd, *J* = 8.2, 2.4, 0.9 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.3, 161.4, 159.2, 138.1, 128.9, 120.7, 118.5, 113.1, 75.6, 55.4, 52.4. **IR:** 3004.5 (w), 2953.5 (w), 2838.2 (w), 2127.8 (m), 1724.9 (m), 1626.8 (m), 1579.9 (m), 1433.4 (m), 1309.6 (s), 1272.2 (s), 1115.6 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{11}H_{10}N_2O_4$, 234.0641; found, 234.0638.



3-12e

Methyl 2-diazo-3-(naphthalen-2-yl)-3-oxopropanoate (3-12e). The general procedure was followed using β-ketoester **3-11e** (5.22 g, 22.9 mmol) in CH_3CN (45.0 mL), triethylamine (2.78 g, 27.5 mmol) and tosyl azide (5.41 g, 27.4 mmol). The reaction mixture was concentrated under reduced pressure and purified via column chromatography to afford diazo **3-12e** (5.30 g, 91%) as a yellow solid (mp: 74-75 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 1.0 Hz, 1H), 7.93 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.85 - 7.90 (m, 2H), 7.69 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.50 - 7.62 (m, 2H), 3.81 ppm (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 186.5, 161.5, 135.2, 134.2, 132.1, 129.6, 129.3, 128.1, 127.8, 127.6, 126.7, 124.6, 76.2, 52.4. **IR:** 3057.5 (w), 2955.1 (w), 2131.6 (m), 1725.5 (s), 1618.8 (m), 1434.7 (m), 1308.5 (s), 1234.2 (m), 1110.2 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{14}H_{10}N_2O_3$, 254.0691; found, 254.0690.

Methyl 2-diazo-3-(3,5-dimethoxyphenyl)-3-oxopropanoate (3-12f).



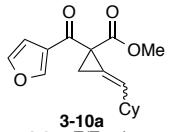
3-12f

Preparation of Methyl 3-(3,5-dimethoxyphenyl)-3-oxopropanoate (**3-11f**). To a solution of LHMDS (1.0 M in THF, 52.0 mL, 52.0 mmol) at -78 °C was added MeOAc (1.91 g, 25.8 mmol) in one shot. The reaction mixture was stirred at -78 °C for 45 min prior the addition of 3,5-dimethoxybenzoyl chloride (4.76 g, 23.7 mmol) in THF (24.0 mL). After stirring for 30 min at -78 °C, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc (3x), dried over Na_2SO_4, and purified via column chromatography (15% Et_2O/hexane, R_f = 0.15) to afford β-ketoester **3-11f** (4.73 g, 84%) as an orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) - keto/enol mixture (1:0.33): δ 12.47 (s, 0.33, minor), 7.04 - 7.08 (m, 2.00, major), 6.90 (d, J = 2.4 Hz, 0.66, minor), 6.65 - 6.68 (m, 1.00, major), 6.55 (t, J = 2.4 Hz, 0.33, minor), 5.63 (s, 0.33, minor), 3.96 (s, 2.00, major), 3.82 (s, 6.00, major), 3.81 (s, 1.98, minor), 3.79 (s, 0.99, minor), 3.75 (s, 3.00, major). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.0, 173.4, 171.3, 167.8, 160.9, 160.8, 137.8, 135.3, 106.3, 106.0, 104.0, 103.6, 87.4, 55.6, 55.4, 52.5, 51.4, 45.8. **IR:** 3088.6 (w), 3004.6 (w), 2951.2 (w), 2840.7 (w), 1740.6 (m), 1683.7 (m), 1589.2 (s), 1455.9 (m), 1426.6 (m), 1322.0 (m), 1203.8 (s), 1151.8 (s), 1062.6 (m), 1007.4 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{12}H_{14}O_5$, 238.0841; found, 238.0846.

Preparation of **3-12f**. The general diazo transfer procedure was followed using β-ketoester **3-11f** (4.06 g, 17.0 mmol) in CH_3CN (34.0 mL) triethylamine (2.07 g, 20.5 mmol) and tosyl azide (4.03 g, 20.4 mmol). The reaction mixture was concentrated under reduced pressure and purified via column chromatography to afford diazo **3-12f** (3.98 g, 89%) as a yellow solid (mp: 100-101 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.75 (d, J = 2.4 Hz, 2H), 6.61 (t, J = 2.4 Hz, 1H), 3.80 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 186.1, 161.3, 160.3 (2C), 138.6, 106.1 (2C), 104.5, 75.7, 55.5 (2C), 52.4. **IR:** 3003.1(w), 2954.2 (w), 2840.7 (w), 2128.6 (m), 1723.7 (m), 1589.2 (s), 1455.4 (m), 1426.3 (m), 1304.3 (s), 1202.9 (s), 1153.9 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{12}H_{12}N_2O_5$, 264.0746; found, 264.0754.

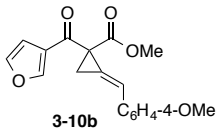
b. Formation of alkylidene cyclopropanes

General Cyclopropanation Procedure: A round bottom flask was charged with Rh_2esp_2 (0.1-0.2 mol %) and CH_2Cl_2 (1.5-2.0 mL). After cooling the solution to 0 °C, the corresponding allene (1.0 equiv.) was added to the reaction vessel. A solution of the α-diazo ester (1.3-1.5 equiv.) in CH_2Cl_2 (1.0 M) was added via syringe pump over 2 hrs, keeping the reaction mixture at 0 °C. After completion of addition, the ice bath was removed and the reaction was allowed to warm up to rt and stirred for 1-2 hr. After complete consumption of the diazo compound, the reaction was quenched with saturated aqueous thiourea and allowed to stir for 30 minutes. The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (2x). The organic layer was washed with brine, dried with Na_2SO_4, concentrated, and column chromatography afforded the desired alkylidene cyclopropane.



3-10a
2.3:1 *E/Z* ratio

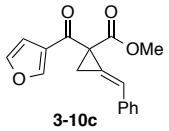
Methyl 2-(cyclohexylmethylene)-1-(furan-3-carbonyl)cyclopropane-1-carboxylate (3-10a). The general procedure was followed using a solution of Rh_2esp_2 (1.3 mg, 1.7 μmol) in CH_2Cl_2 (2.0 mL), allene **3-13a** (210 mg, 1.72 mmol), and diazo **3-12a** (500 mg, 2.58 mmol) in CH_2Cl_2 (2.6 mL). The reaction was quenched and column chromatography (10% Et_2O/hexane, R_f = 0.14) afforded **3-10a** (287 mg, 58%) as a white solid (mp: 61-63 °C). *Diasteromeric mixture*: (2.3:1 *E*/*Z* ratio). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 1.4, 0.9 Hz, 0.43, minor), 8.00 (dd, *J* = 1.5, 0.8 Hz, 1.00, major), 7.42 (dd, *J* = 2.0, 1.5 Hz, 1.00, major), 7.41 (dd, *J* = 1.9, 1.4 Hz, 0.43, minor), 6.72 - 6.76 (m, 1.43, major + minor), 5.89 - 5.94 (m, 1.00, major), 5.86 (dt, *J* = 8.3, 2.4 Hz, 0.43, minor), 3.72 (s, 1.29, minor), 3.67 (s, 3.00, major), 2.14 - 2.34 (m, 3.86, major + minor), 2.10 (ddd, *J* = 8.7, 2.4, 1.0 Hz, 0.43, minor), 1.76 - 1.87 (m, 2.00, major), 1.56 - 1.76 (m, 5.15, major + minor), 1.06 - 1.35 (m, 7.15, major + minor). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 187.1, 186.3, 170.4, 170.0, 147.7, 147.3, 143.8, 143.6, 127.5, 126.6, 126.6, 126.1, 119.7, 119.7, 109.3, 109.2, 52.6, 52.6, 40.5, 39.8, 38.2, 36.8, 32.3, 32.2, 26.0, 25.9, 25.8, 25.7, 18.1, 17.4. **IR:** 3145.3 (w), 2924.3 (m), 2850.7 (m), 1725.8 (s), 1672.2 (s), 1561.0 (m), 1507.8 (m), 1389.4 (m), 1310.4 (s), 1154.6 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{17}H_{20}O_4$, 288.1362; found, 288.1360.



3-10b

Methyl (*E*)-1-(furan-3-carbonyl)-2-(4-methoxybenzylidene)cyclopropane-1-carboxylate (3-10b). The general procedure was followed using a solution of Rh_2esp_2 (2.6 mg, 3.4 μmol)

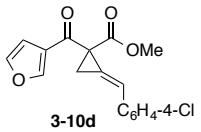
in CH_2Cl_2 (2.0 mL), allene **3-13b** (258 mg, 1.76 mmol), and diazo **3-12a** (502 mg, 2.59 mmol) in CH_2Cl_2 (2.6 mL). The reaction was quenched and column chromatography (25% Et_2O/hexane, R_f = 0.24) afforded **3-10b** (180 mg, 33%) as a yellow solid (mp: 71-73 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.08 (dd, *J* = 1.5, 0.9 Hz, 1H), 7.45 - 7.47 (m, 1H), 7.42 - 7.45 (m, 2H), 6.87 - 6.90 (m, 2H), 6.84 (t, *J* = 2.4 Hz, 1H), 6.79 (dd, *J* = 2.0, 0.9 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 2.55 (dd, *J* = 9.5, 2.4 Hz, 1H), 2.47 (dd, *J* = 9.5, 2.4 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 185.9, 170.1, 159.7, 147.8 (2C), 143.9, 128.7, 128.3, 126.4, 120.1, 119.8, 114.1 (2C), 109.2, 55.3, 52.8, 36.2, 18.2. **IR:** 3133.38 (w), 2954.7 (w), 2838.1 (w), 1722.3 (m), 1671.1 (m), 1510.3 (s), 1246.9 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{18}H_{16}O_5$, 312.0998; found, 312.1003.



3-10c

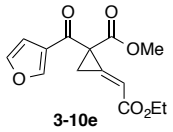
Methyl (*E*)-2-benzylidene-1-(furan-3-carbonyl)cyclopropane-1-carboxylate (3-10c). The general procedure was followed using a solution of Rh_2esp_2 (2.7 mg, 3.6 μmol) in CH_2Cl_2 (2.0 mL), allene **3-13c** (200 mg, 1.72 mmol), and diazo **3-12a** (503 mg, 2.59 mmol) in CH_2Cl_2 (2.6 mL). The reaction was quenched and column chromatography (25% Et_2O/hexane, R_f = 0.33) afforded **3-10c** (166 mg, 34%) as a white solid (mp: 122-124 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.08 - 8.10 (m, 1H), 7.51 (d, *J* = 7.3 Hz, 2H), 7.47 (t, *J* = 1.7 Hz, 1H), 7.33 - 7.38 (m, 2H), 7.26 - 7.31 (m, 1H), 6.90 (t, *J* = 2.6 Hz, 1H), 6.80 (dd, *J* = 1.8, 0.6 Hz, 1H), 3.73 (s, 3H), 2.59 (dd, *J* = 9.6, 2.6 Hz, 1H), 2.51 (dd, *J* = 9.6, 2.6 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 185.6, 169.9, 147.8, 144.0, 135.5 (2C), 128.6, 128.2 (2C), 127.4, 126.4, 122.1, 120.6, 109.2, 52.8, 36.1, 18.2. **IR:** 3142.4 (w), 3030.3 (w), 2954.4 (w), 1724.4

(s), 1672.5 (s), 1560.5 (m), 1507.8 (m), 1313.2 (m), 1259.6 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{17}H_{14}O_4$, 282.0892; found, 282.0887.



3-10d

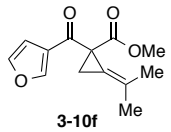
Methyl (*E*)-2-(4-chlorobenzylidene)-1-(furan-3-carbonyl)cyclopropane-1-carboxylate (3-10d). The general procedure was followed using a solution of Rh_2esp_2 (2.7 mg, 3.6 μmol) in CH_2Cl_2 (2.0 mL), allene **3-13d** (257 mg, 1.71 mmol), and diazo **3-12a** (502 mg, 2.59 mmol) in CH_2Cl_2 (2.6 mL). The reaction was quenched and column chromatography (20% Et_2O/hexane, R_f = 0.20) afforded **3-10d** (157 mg, 29%) as a yellow solid (mp: 78-80 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.07 - 8.10 (m, 1H), 7.47 (t, *J* = 1.7 Hz, 1H), 7.41 - 7.45 (m, 2H), 7.30 - 7.34 (m, 2H), 6.85 (t, *J* = 2.4 Hz, 1H), 6.79 (dd, *J* = 1.7, 0.6 Hz, 1H), 3.73 (s, 3H), 2.56 (dd, *J* = 9.8, 2.4 Hz, 1H), 2.48 (dd, *J* = 9.8, 2.4 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 185.3, 169.8, 147.9, 144.1, 134.1, 134.0, 128.9 (2C), 128.6 (2C), 126.4, 122.7, 119.5, 109.1, 52.9, 36.1, 18.0. **IR:** 3138.6 (w), 2953.3 (w), 1725.4 (s), 1672.5 (s), 1491.9 (m), 1310.9 (m), 1259.2 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{17}H_{13}O_4Cl$, 316.0502; found, 316.0505.



3-10e

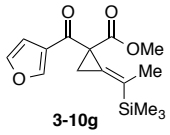
Methyl (*E*)-2-(2-ethoxy-2-oxoethylidene)-1-(furan-3-carbonyl)cyclopropane-1-carboxylate (3-10e). The general procedure using a solution of Rh_2esp_2 (1.3 mg, 1.7 μmol) in CH_2Cl_2 (2.0 mL), allene **3-13e** (197 mg, 1.76 mmol), and diazo **3-12a** (510 mg, 2.63

mmol) in CH_2Cl_2 (2.6 mL). The reaction was quenched and column chromatography (20% Et_2O/hexane, R_f = 0.17) afforded **3-10e** (83.9 mg, 17%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.24 (dd, *J* = 1.5, 0.6 Hz, 1H), 7.40 - 7.43 (m, 1H), 6.82 (dd, *J* = 1.8, 0.6 Hz, 1H), 6.30 (t, *J* = 2.3 Hz, 1H), 4.18 (qd, *J* = 7.2, 1.2 Hz, 2H), 3.73 (s, 3H), 2.47 (dd, *J* = 10.7, 2.3 Hz, 1H), 2.28 (dd, *J* = 10.7, 2.3 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 184.0, 168.6, 164.3, 149.2, 143.4, 138.9, 126.0, 112.2, 109.5, 60.8, 52.9, 38.3, 16.3, 14.1. **IR:** 3133.9 (w), 2984.0 (w), 2957.5 (w), 1726.8 (s), 1663.5 (m), 1436.1 (m), 1369.6 (m), 1330.2 (m), 1278.4 (m), 1180.0 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{14}H_{14}O_6$, 278.0790; found, 278.0793.



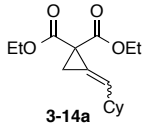
3-10f

Methyl 1-(furan-3-carbonyl)-2-(propan-2-ylidene)cyclopropane-1-carboxylate (3-10f). The general procedure was followed using a solution of Rh_2esp_2 (1.4 mg, 1.8 μmol) in CH_2Cl_2 (2.0 mL), allene **3-13f** (118 mg, 1.73 mmol), and diazo **3-12a** (508 mg, 2.62 mmol) in CH_2Cl_2 (2.6 mL). The reaction was quenched and column chromatography (15% Et_2O/hexane, R_f = 0.26) afforded **3-10f** (239 mg, 59%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.41 (t, *J* = 1.7 Hz, 1H), 6.73 - 6.76 (m, 1H), 3.72 (s, 3H), 2.20 - 2.27 (m, 1H), 2.06 - 2.12 (m, 1H), 1.90 - 1.92 (m, 3H), 1.88 (t, *J* = 2.0 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 187.7, 170.2, 147.2, 143.6, 126.3, 126.2, 116.5, 109.3, 52.6, 39.0, 22.4, 21.9, 18.6. **IR:** 3136.3 (w), 2978.4 (w), 2952.7 (w), 2914.5 (w), 2861.0 (w), 1723.7 (s), 1670.1 (s), 1560.6 (m), 1507.3 (m), 1436.1 (m), 1273.2 (s), 1161.3 (s), 1088.6 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{13}H_{14}O_4$, 234.0892; found, 234.0890.



3-10g

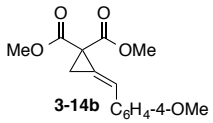
Methyl (*E*)-1-(furan-3-carbonyl)-2-(1-(trimethylsilyl)ethylidene)cyclopropane-1-carboxylate (3-10g). The general procedure was followed using a solution of Rh_2esp_2 (1.5 mg, 2.0 μmol) in CH_2Cl_2 (2.0 mL), allene **3-13g** (220 mg, 1.74 mmol), and diazo **3-12a** (512 mg, 2.64 mmol) in CH_2Cl_2 (2.6 mL). The reaction was quenched and column chromatography (15% Et_2O/hexane, R_f = 0.32) afforded **3-10g** (279 mg, 55%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.00 (dd, *J* = 1.5, 0.9 Hz, 1H), 7.40 - 7.41 (m, 1H), 6.75 (dd, *J* = 2.0, 0.9 Hz, 1H), 3.72 (s, 3H), 2.35 (dq, *J* = 9.0, 2.2 Hz, 1H), 2.25 (dq, *J* = 9.0, 2.2 Hz, 1H), 1.91 (t, *J* = 2.2 Hz, 3H), 0.15 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 187.4, 169.9, 147.2, 143.6, 128.8, 127.9, 126.3, 109.4, 52.6, 37.5, 19.6, 18.9, -2.0 (3C). **IR:** 3153.9 (w), 2954.1 (w), 2897.8 (w), 2853.9 (w), 1725.6 (m), 1660.4 (m), 1507.8 (m), 1435.2 (m), 1386.5 (m), 1263.1 (m), 1192.9 (m), 1083.1 (m), 748.0 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{15}H_{20}O_4Si$, 292.1131; found, 292.1140.



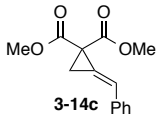
3-14a
5.3:1.0 *E/Z* ratio

Diethyl 2-(cyclohexylmethylene)cyclopropane-1,1-dicarboxylate (3-14a). According to the general cyclopropanation procedure, to a solution of Rh_2esp_2 (2.7 mg, 3.6 μmol) in CH_2Cl_2 (2.0 mL) at 0 °C was added allene **3-13a** (219 mg, 1.79 mmol) followed by the addition of diazo **3-12g** (503 mg, 2.70 mmol) in CH_2Cl_2 (2.7 mL) over 2 hrs via syringe pump. The reaction was quenched and column chromatography (15% Et_2O/hexane, R_f =

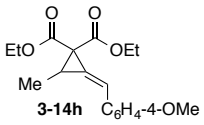
0.39) afforded **3-14a** (256 mg, 51%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) - Diasteromeric mixture (*E*/*Z* 5.3:1.0): δ 5.93 - 5.99 (m, 1.00, major), 5.76 - 5.81 (m, 0.19, minor), 4.14 - 4.21 (m, 4.76, major + minor), 2.18 - 2.27 (m, 1.19, major + minor), 2.16 (dd, *J* = 2.7, 1.8 Hz, 2.00, major), 2.11 (dd, *J* = 2.3, 1.1 Hz, 0.38, minor), 1.77 - 1.88 (m, 2.00, major), 1.60 - 1.76 (m, 3.95, major + minor), 1.13 - 1.33 ppm (m, 13.09, major + minor). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.3, 168.3, 126.3, 126.0, 120.1, 119.9, 61.4, 40.5, 39.6, 32.2, 32.2, 30.9, 26.1, 26.0, 25.9, 25.8, 18.3, 17.6, 14.1, 14.0. **IR:** 2980.0 (w), 2931.0 (m), 2854.2 (w), 1728.4 (s), 1447.3 (m), 1368.7 (m), 1251.7 (s), 1095.6 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{16}H_{24}O_4$, 280.1675; found, 280.1668.



Dimethyl (*E*)-2-(4-methoxybenzylidene)cyclopropane-1,1-dicarboxylate (3-14b). The general cyclopropanation procedure was followed using a solution of Rh_2esp_2 (3.3 mg, 4.4 μmol) in CH_2Cl_2 (2.0 mL), allene **3-13b** (308 mg, 2.11 mmol), and diazo **3-12c** (507 mg, 3.21 mmol) in CH_2Cl_2 (3.2 mL). The reaction was quenched and column chromatography (20% Et_2O/hexane, R_f = 0.10) afforded **3-14b** (447 mg, 77%) as a white solid (mp: 95-96 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.42 - 7.46 (m, 2H), 6.87 - 6.91 (m, 3H), 3.82 (s, 3H), 3.75 (s, 6H), 2.47 (d, *J* = 2.7 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.4 (2C), 159.6, 128.7 (2C), 128.4, 120.1, 119.8, 114.1 (2C), 55.3, 52.8 (2C), 30.1, 19.3. **IR:** 3000.9 (w), 2954.5 (w), 2840.1 (w), 1730.5 (s), 1606.1 (m), 1512.7 (m), 1435.8 (m), 1249.6 (s), 1103.6 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{15}H_{16}O_5$, 276.0998; found, 276.1005.

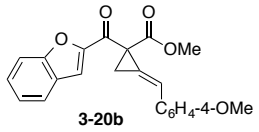


Dimethyl (*E*)-2-benzylidenecyclopropane-1,1-dicarboxylate (3-14c). The general cyclopropanation procedure was followed using a solution of Rh_2esp_2 (3.3 mg, 4.4 μmol) in CH_2Cl_2 (2.0 mL), allene **3-13c** (245 mg, 2.11 mmol), and diazo **3-12c** (509 mg, 3.22 mmol) in CH_2Cl_2 (3.2 mL). The reaction was quenched and column chromatography (20% Et_2O/hexane, R_f = 0.24) afforded **3-14c** (425 mg, 82%) as a light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.50 - 7.53 (m, 2H), 7.34 - 7.39 (m, 2H), 7.26 - 7.31 (m, 1H), 6.94 (t, *J* = 2.7 Hz, 1H), 3.76 (s, 6H), 2.51 (d, *J* = 2.7 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.2 (2C), 135.5, 128.6 (2C), 128.2, 127.5 (2C), 122.4, 120.3, 52.8 (2C), 30.0, 19.3. **IR:** 3009.1 (w), 2953.8 (w), 1730.9 (s), 1436.0 (m), 1255.1 (m), 1104.8 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{14}H_{14}O_4$, 246.0892; found, 246.0898.



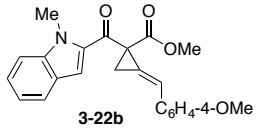
Diethyl (*E*)-2-(4-methoxybenzylidene)-3-methylcyclopropane-1,1-dicarboxylate (3-14h). According to the general cyclopropanation procedure, to a solution of Rh_2esp_2 (3.0 mg, 4.0 μmol) in CH_2Cl_2 (2.0 mL) at 0 °C was added racemic allene **3-13h** (283 mg, 1.77 mmol) followed by the addition of diazo **3-12g** (506 mg, 2.72 mmol) in CH_2Cl_2 (2.7 mL) over 2 hrs via syringe pump. The reaction was quenched and column chromatography (10% Et_2O/hexane, R_f = 0.09) afforded **3-14h** (423 mg, 75%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.34 - 7.39 (m, 2H), 6.87 - 6.91 (m, 2H), 6.86 (d, *J* = 2.4 Hz, 1H), 4.15 - 4.30 (m, 4H), 3.81 (s, 3H), 2.88 (qd, *J* = 6.5, 2.4 Hz, 1H), 1.35 (d, *J* = 6.5 Hz, 3H), 1.22 - 1.34 ppm

(m, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.6 (2C), 166.8, 159.4, 128.7 (2C), 125.7, 120.1, 114.1 (2C), 61.7, 61.4, 55.3, 35.9, 25.5, 19.7, 14.0 (2C). **IR:** 2981.5 (w), 2935.3 (w), 2837.5 (w), 1831.1 (m), 1720.7 (s), 1606.2 (m), 1512.3 (m), 1242.8 (s), 1098.3 (m), 1021.9 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{18}H_{22}O_5$, 318.1467; found, 318.1461.



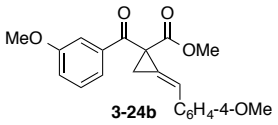
3-20b

Methyl (*E*)-1-(benzofuran-2-carbonyl)-2-(4-methoxybenzylidene)cyclopropane-1-carboxylate (3-20b). The general procedure was followed using a solution of Rh_2esp_2 (2.2 mg, 2.9 μmol) in CH_2Cl_2 (2.0 mL), allene **3-13b** (199 mg, 1.36 mmol), and diazo **3-12b** (498 mg, 2.04 mmol) in CH_2Cl_2 (2.0 mL). The reaction was quenched and column chromatography (20% EtOAc/hexane, R_f = 0.31) afforded **3-20b** (400 mg, 81%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.9 Hz, 1H), 7.63 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.60 (d, *J* = 0.9 Hz, 1H), 7.51 (ddd, *J* = 8.5, 7.9, 0.9 Hz, 1H), 7.42 - 7.48 (m, 2H), 7.31 - 7.38 (m, 1H), 6.98 (t, *J* = 2.6 Hz, 1H), 6.86 - 6.90 (m, 2H), 3.81 (s, 3H), 3.71 (s, 3H), 2.65 (dd, *J* = 9.5, 2.6 Hz, 1H), 2.52 (dd, *J* = 9.5, 2.6 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 182.0, 170.1, 159.7, 155.8, 152.2, 128.8 (2C), 128.4 (2C), 127.1, 124.0, 123.4, 120.6, 119.7, 114.1 (2C), 113.8, 112.5, 55.3, 52.8, 35.0, 18.0. **IR:** 3057.1 (w), 3005.7 (w), 2952.7 (w), 2837.6 (w), 1792.7 (m), 1723.2 (m), 1605.8 (m), 1511.1 (m), 1435.5 (m), 1247.4 (s), 1109.6 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{22}H_{18}O_5$, 362.1154; found, 362.1165.



3-22b

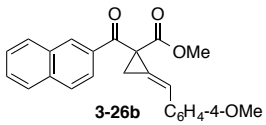
Methyl (E)-2-(4-methoxybenzylidene)-1-(1-methyl-1*H*-indole-2-carbonyl)cyclopropane-1-carboxylate (3-22b): To a solution of *N*-methylindole (143 mg, 1.09 mmol) in Et_2O (4.5 mL) at 0 °C was added *n*-BuLi (2.5 M in hexane, 0.43 mL, 1.1 mmol) and stirred for 15 min at 0 °C prior refluxing for 3 hrs. The reaction mixture was then cooled to -78 °C and a solution of cyclopropane **3-14b** (151 mg, 0.547 mmol) in THF (2.3 mL) was added in one shot and stirred for 10 min. At this point, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc (2x), dried over Na_2SO_4, and purified via column chromatography (20% EtOAc/hexane, R_f = 0.30) to afford **3-22b** (137 mg, 67%) as a yellow solid (mp: 135-137 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 8.9 Hz, 2H), 7.40 - 7.42 (m, 2H), 7.38 (s, 1H), 7.19 (dt, *J* = 8.2, 4.0 Hz, 1H), 6.94 (t, *J* = 2.6 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 4.09 (s, 3H), 3.82 (s, 3H), 3.69 (s, 3H), 2.60 (dd, *J* = 9.3, 2.6 Hz, 1H), 2.48 (dd, *J* = 9.3, 2.6 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 184.3, 170.8, 159.5, 140.2, 134.0, 128.7 (2C), 128.6, 126.2, 126.0, 123.2, 120.9, 120.3, 120.0, 114.0 (2C), 112.9, 110.4, 55.3, 52.8, 36.0, 32.1, 18.1. **IR:** 2949.8 (w), 1725.8 (m), 1655.3 (m), 1606.4 (w), 1511.8 (s), 1250.0, 1114.2 (s). **HRMS** (EI) *m/z*: [M-Na^+] calcd. for $C_{23}H_{21}O_4NNa$, 398.1363; found, 398.1350.



3-24b

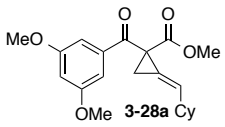
Methyl (*E*)-1-(3-methoxybenzoyl)-2-(4-methoxybenzylidene)cyclopropane-1-carboxylate (3-24b). The general procedure was followed using a solution of Rh_2esp_2 (2.2 mg, 2.9 μmol) in CH_2Cl_2 (2.0 mL), allene **3-13b** (210 mg, 1.44 mmol), and diazo **3-12d** (506 mg, 2.16 mmol) in CH_2Cl_2 (2.2 mL). The reaction was quenched and column

chromatography (20% Et_2O/hexane, R_f = 0.13) afforded **3-24b** (322 mg, 63%) as a light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.58 (dq, *J* = 7.6, 0.8 Hz, 1H), 7.53 (dd, *J* = 2.6, 1.7 Hz, 1H), 7.41 - 7.47 (m, 3H), 7.14 (ddd, *J* = 8.2, 2.6, 0.8 Hz, 1H), 6.86 - 6.91 (m, 3H), 3.87 (s, 3H), 3.81 (s, 3H), 3.65 (s, 3H), 2.62 (dd, *J* = 9.5, 2.4 Hz, 1H), 2.47 (dd, *J* = 9.5, 2.4 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 191.0, 170.7, 159.9, 159.6, 137.3, 129.6 (2C), 128.7, 128.5, 121.7, 120.3, 120.0, 119.8, 114.1 (2C), 113.0, 55.5, 55.3, 52.7, 35.0, 18.2. **IR:** 3003.5 (w), 2954.1 (w), 2837.2 (w), 1792.1 (m), 1723.5 (m), 1604.5 (m), 1511.7 (m), 1249.1 (s), 1032.4 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{21}H_{20}O_5$, 352.1311; found, 352.1302.

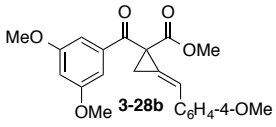


Methyl (*E*)-1-(2-naphthoyl)-2-(4-methoxybenzylidene)cyclopropane-1-carboxylate (3-26b). The general procedure was followed using a solution of Rh_2esp_2 (1.4 mg, 1.8 μmol) in CH_2Cl_2 (1.5 mL), allene **3-13b** (132 mg, 0.903 mmol), and diazo **3-12e** (311 mg, 1.22 mmol) in CH_2Cl_2 (1.7 mL). The reaction was quenched and column chromatography (20% Et_2O/hexane, R_f = 0.14) afforded **3-26b** (203 mg, 60%) as a light yellow solid (mp: 95-97 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.06 (dd, *J* = 8.5, 1.8 Hz, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.61 - 7.66 (m, 1H), 7.56 - 7.61 (m, 1H), 7.46 (d, *J* = 8.9 Hz, 2H), 6.94 (t, *J* = 2.6 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H), 3.65 (s, 3H), 2.68 (dd, *J* = 9.5, 2.6 Hz, 1H), 2.55 (dd, *J* = 9.5, 2.6 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 191.1, 170.8, 159.6, 135.7, 133.4, 132.6, 130.8, 129.7, 128.7 (2C), 128.7, 128.6, 128.5, 127.8, 126.9, 124.5, 120.4, 120.2, 114.1 (2C), 55.3, 52.8, 35.1, 18.3. **IR:**

3058.5 (w), 3001.0 (w), 2953.4 (w), 2837.0 (w), 1790.0 (m), 1724.0 (m), 1511.4 (m), 1249.1 (s), 1109.9 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{24}H_{20}O_4$, 372.1362; found, 372.1361.

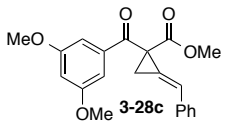


Methyl (*E*)-2-(cyclohexylmethylene)-1-(3,5-dimethoxybenzoyl)cyclopropane-1-carboxylate (3-28a). The general procedure was followed using a solution of Rh_2esp_2 (1.0 mg, 1.3 μmol) in CH_2Cl_2 (2.0 mL), allene **3-13a** (160 mg, 1.31 mmol), and diazo **3-12f** (503 mg, 1.90 mmol) in CH_2Cl_2 (1.9 mL). The reaction was quenched and column chromatography (20% Et_2O/hexane, R_f = 0.30) afforded **3-28a** (342 mg, 73%) as a light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.06 (d, *J* = 2.1 Hz, 2H), 6.65 (t, *J* = 2.3 Hz, 1H), 5.94 - 5.98 (m, 1H), 3.83 (s, 6H), 3.62 (s, 3H), 2.33 - 2.37 (m, 1H), 2.20 - 2.28 (m, 1H), 2.15 - 2.19 (m, 1H), 1.77 - 1.87 (m, 2H), 1.68 - 1.76 (m, 2H), 1.60 - 1.68 (m, 1H), 1.12 - 1.34 (m, 5H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 191.5, 170.8, 160.8 (2C), 138.1, 126.8, 119.8, 106.7 (2C), 105.4, 55.6 (2C), 52.5, 39.9, 35.7, 32.2 (2C), 26.1, 25.9 (2C), 17.4. **IR:** 2923.7 (m), 2849.3 (w), 1726.3 (m), 1680.9 (m), 1591.2 (m), 1426.6 (m), 1319.1 (m), 1155.1 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{21}H_{26}O_5$, 358.1780; found, 358.1789.



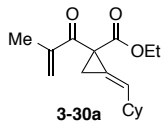
Methyl (*E*)-1-(3,5-dimethoxybenzoyl)-2-(4-methoxybenzylidene)cyclopropane-1-carboxylate (3-28b). The general procedure was followed using a solution of Rh_2esp_2 (1.5 mg, 2.0 μmol) in CH_2Cl_2 (1.5 mL), allene **3-13b** (129 mg, 0.882 mmol), and diazo **3-12f** (305

mg, 1.15 mmol) in CH_2Cl_2 (1.7 mL) over 2 hrs via syringe pump. The reaction was quenched and column chromatography (35% Et_2O/hexane, R_f = 0.21) afforded **3-28b** (130 mg, 39%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 2.1 Hz, 2H), 6.86 - 6.91 (m, 3H), 6.68 (t, *J* = 2.6 Hz, 1H), 3.85 (s, 6H), 3.81 (s, 3H), 3.66 (s, 3H), 2.60 (dd, *J* = 9.3, 2.6 Hz, 1H), 2.46 (dd, *J* = 9.3, 2.6 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 190.9, 170.5, 160.9 (2C), 159.6, 137.9 (2C), 128.7, 128.4, 120.3, 119.9, 114.0 (2C), 106.8 (2C), 105.5, 55.6 (2C), 55.3, 52.7, 35.0, 18.2. **IR:** 3003.1 (w), 2953.5 (w), 2837.8 (w), 1723.4 (m), 1679.6 (m), 1591.6 (m), 1511.4 (m), 1426.3 (m), 1298.7 (m), 1247.9 (s), 1155.2 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{22}H_{22}O_6$, 382.1416; found, 382.1412.



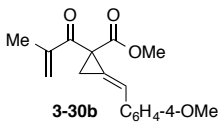
Methyl (*E*)-2-benzylidene-1-(3,5-dimethoxybenzoyl)cyclopropane-1-carboxylate (3-28c). The general procedure was followed using a solution of Rh_2esp_2 (1.8 mg, 2.4 μmol) in CH_2Cl_2 (2.0 mL), allene **3-13c** (91.6 mg, 0.786 mmol), and diazo **3-12f** (304 mg, 1.15 mmol) in CH_2Cl_2 (1.2 mL). The reaction was quenched and column chromatography (20% Et_2O/hexane, R_f = 0.17) afforded **3-28c** (194 mg, 70%) as a light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.49 - 7.54 (m, 2H), 7.32 - 7.38 (m, 2H), 7.25 - 7.29 (m, 1H), 7.15 (d, *J* = 2.1 Hz, 2H), 6.94 (t, *J* = 2.7 Hz, 1H), 6.69 (t, *J* = 2.3 Hz, 1H), 3.86 (s, 6H), 3.67 (s, 3H), 2.64 (dd, *J* = 9.5, 2.7 Hz, 1H), 2.50 (dd, *J* = 9.5, 2.7 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 190.7, 170.4, 160.9 (2C), 137.8, 135.6, 128.6 (2C), 128.1, 127.4 (2C), 122.2, 120.9, 106.8 (2C), 105.5, 55.6 (2C), 52.8, 35.0, 18.2. **IR:** 3001.8 (w), 2952.6 (w), 2839.0 (w), 1724.6 (m),

1681.1 (m), 1591.7 (m), 1454.4 (m), 1427.1 (m), 1319.9 (m), 1155.8 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{21}H_{20}O_5$, 352.1311; found, 352.1299.



3-30a

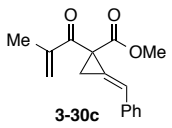
Ethyl (*E*)-2-(cyclohexylmethylene)-1-methacryloylcyclopropane-1-carboxylate (30a). To a solution of cyclopropane **3-14a** (109 mg, 0.389 mmol) in THF (1.9 mL) at -78 °C was added isoprenylmagnesium bromide (0.5 M in THF, 0.93 mL, 0.47 mmol). After stirring for 90 min at -78 °C, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc (2x), dried over Na_2SO_4, and purified via column chromatography (10% Et_2O/hexane, R_f = 0.27) to afford **3-30a** (90.5 mg, 84%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.89 - 5.92 (m, 1H), 5.83 - 5.86 (m, 1H), 5.82 (dd, *J* = 1.5, 0.6 Hz, 1H), 4.06 - 4.24 (m, 2H), 2.17 - 2.26 (m, 2H), 2.02 - 2.07 (m, 1H), 1.93 (dd, *J* = 1.5, 0.9 Hz, 3H), 1.77 - 1.85 (m, 2H), 1.68 - 1.75 (m, 2H), 1.60 - 1.67 (m, 1H), 1.23 - 1.34 (m, 3H), 1.12 - 1.23 (m, 5H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 193.9, 170.4, 143.9, 126.2, 125.5, 120.0, 61.3, 39.7, 35.3, 32.3 (2C), 26.1, 25.9 (2C), 17.7, 17.2, 13.9. **IR:** 2978.4 (w), 2924.4 (m), 2851.4 (m), 1721.0 (s), 1678.5 (s), 1448.1 (m), 1252.2 (s), 1125.5 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{17}H_{24}O_3$, 276.1725; found, 276.1725.



3-30b

Methyl (*E*)-1-methacryloyl-2-(4-methoxybenzylidene)cyclopropane-1-carboxylate (3-30b). To a solution of cyclopropane **3-14b** (100 mg, 0.362 mmol) in THF (1.8 mL) at -78 °C

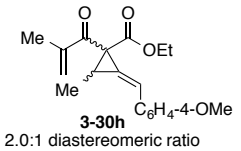
was added isoprenylmagnesium bromide (0.5 M in THF, 0.87 mL, 0.44 mmol). After stirring for 1 hr at -78 °C, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc (2x), dried over Na_2SO_4, and purified via column chromatography (20% Et_2O/hexane, R_f = 0.18) to afford **3-30b** (82.4 mg, 79%) as a light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 - 7.46 (m, 2H), 6.86 - 6.91 (m, 2H), 6.77 (t, *J* = 2.6 Hz, 1H), 6.03 - 6.05 (m, 1H), 5.92 - 5.94 (m, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 2.48 (dd, *J* = 9.3, 2.6 Hz, 1H), 2.34 (dd, *J* = 9.3, 2.6 Hz, 1H), 1.96 (dd, *J* = 1.5, 0.9 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 193.0, 170.7, 159.6, 143.7, 128.6 (2C), 128.5, 126.2, 120.1, 119.9, 114.1 (2C), 55.3, 52.6, 34.4, 18.0, 17.7. **IR:** 2952.9 (w), 2839.0 (w), 1723.7 (m), 1605.5 (m), 1511.7 (m), 1247.4 (s), 1173.78 (m), 1030.9 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{17}H_{18}O_5$, 286.1205; found, 286.1197.



3-30c

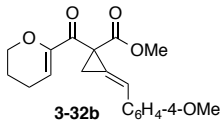
Methyl (*E*)-2-benzylidene-1-methacryloylcyclopropane-1-carboxylate (3-30c). To a solution of cyclopropane **3-14c** (198 mg, 0.804 mmol) in THF (4.0 mL) at -78 °C was added isoprenylmagnesium bromide (0.5 M in THF, 2.0 mL, 1.0 mmol). After stirring for 1 hr at -78 °C, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc (2x), dried over Na_2SO_4, and purified via column chromatography (20% Et_2O/hexane, R_f = 0.30) to afford **3-30c** (154 mg, 75%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 1H), 6.83 (t, *J* = 2.7 Hz, 1H), 6.06 (s, 1H), 5.93 - 5.96 (s, 1H), 3.71 (s, 3H), 2.51 (dd, *J* = 9.5, 2.7 Hz, 1H), 2.38 (dd, *J* = 9.5, 2.7 Hz, 1H), 1.96 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.7, 170.5, 143.6, 135.7, 128.6 (2C), 128.1, 127.4 (2C), 126.3, 122.4, 120.4, 52.7, 34.4, 18.1, 17.7. **IR:** 3033.9 (w), 2954.7

(w), 1724.9 (s), 1436.3 (m), 1262.8 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{16}H_{16}O_3$, 256.1099; found, 256.1110.

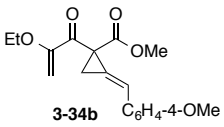


3-30h
2.0:1 diastereomeric ratio

Ethyl (*E/Z*)-1-methacryloyl-2-(4-methoxybenzylidene)-3-methylcyclopropane-1-carboxylate (3-30h). To a solution of cyclopropane **3-14h** (154 mg, 0.484 mmol) in THF (2.4 mL) at -78 °C was added isoprenylmagnesium bromide (0.5 M in THF, 1.1 mL, 0.55 mmol). After stirring for 1 hr at -78 °C, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc (2x), dried over Na_2SO_4, and purified via column chromatography (15% Et_2O/hexane, R_f = 0.23) to afford **3-30h** (70.7 mg, 47%) as a yellow oil. *Diasteromeric mixture*: (2:1 *E*/*Z* ratio). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.32 - 7.39 (m, 3.00, major + minor), 6.86 - 6.91 (m, 3.50, major + minor), 6.69 (d, *J* = 2.4 Hz, 1.00, major), 6.03 (s, 1.00, major), 5.96 (s, 0.50, minor), 5.84 - 5.88 (m, 1.50, major + minor), 4.11 - 4.23 (m, 3.00, major + minor), 3.81 (s, 4.50, major + minor), 2.94 - 3.05 (m, 1.50, major + minor), 1.92 - 1.97 (m, 4.50, major + minor), 1.37 - 1.41 (m, 3.00, major), 1.18 - 1.25 (m, 6.00, major + minor). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 194.2, 193.1, 169.7, 168.7, 159.4, 159.3, 145.5, 144.3, 128.8, 128.7, 128.6, 125.9, 125.6, 125.3, 125.0, 120.6, 119.9, 114.1, 114.0, 61.6, 61.4, 55.3, 40.8, 38.9, 26.0, 23.0, 17.8, 17.6, 14.2, 14.0, 12.3, 11.1. **IR:** 2964.07 (w), 2931.5 (w), 2838.4 (w), 1726.5 (m), 1675.8 (m), 1511.8 (m), 1452.4 (m), 1246.5 (s), 1028.8 (m). **HRMS** (EI) *m/z*: [M+] calcd. for $C_{19}H_{22}O_4$, 314.1518; found, 314.1530.



Methyl (*E*)-1-(3,4-dihydro-2*H*-pyran-6-carbonyl)-2-(4-methoxybenzylidene)cyclopropane-1-carboxylate (3-32b). To a solution of 3,4-dihydropyran (163 mg, 1.94 mmol) in THF (5.0 mL) at -78 °C was added *t*-BuLi (1.7 M in pentane, 1.1 mL, 1.9 mmol). The reaction mixture was then warmed up to 0 °C, stirred for 30 min, and then cooled to -78 °C prior addition of cyclopropane **3-14b** (149 mg, 0.539 mmol) in THF (2.2 mL). After stirring for 20 min at -78 °C, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc (2x), dried over Na_2SO_4, and purified via column chromatography (20% EtOAc/hexane, R_f = 0.21) to afford **3-32b** (112 mg, 63%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.39 - 7.48 (m, 2H), 6.86 - 6.91 (m, 2H), 6.84 (t, *J* = 2.7 Hz, 1H), 6.05 (t, *J* = 4.3 Hz, 1H), 4.13 - 4.20 (m, 1H), 4.08 (dd, *J* = 7.2, 3.5 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 2.47 (dd, *J* = 9.5, 2.7 Hz, 1H), 2.29 (dd, *J* = 9.5, 2.7 Hz, 1H), 2.23 - 2.28 (m, 2H), 1.85 - 1.96 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 187.8, 170.3, 159.5, 150.6, 128.7, 128.7 (2C), 120.2, 119.8, 114.0 (2C), 110.8, 66.4, 55.3, 52.4, 34.3, 21.8, 20.8, 17.4. **IR:** 2952.6 (w), 2837.5 (w), 1724.6 (w), 1693.7 (w), 1511.6 (m), 1435.6 (w), 1247.7 (s), 1173.2 (m), 1120.7 (m), 1029.7 (m). **HRMS** (ESI) *m/z*: [M-H$^+$] calcd. for $C_{19}H_{21}O_5$, 329.1384; found, 329.1380.



Methyl (*E*)-1-(2-ethoxyacryloyl)-2-(4-methoxybenzylidene)cyclopropane-1- carboxylate (3-34b). To a solution of ethyl vinyl ether (190 mg, 2.63 mmol) in THF (5.0 mL) at -78 °C

was added *t*-BuLi (1.7 M in pentane, 1.4 mL, 2.4 mmol). The reaction mixture was then warmed up to 0 °C, stirred for 30 min, and then cooled to -78 °C prior addition of cyclopropane **3-14b** (200 mg, 0.722 mmol) in THF (3.0 mL). After stirring for 25 min at -78 °C, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc (2x), dried over Na_2SO_4, and purified via column chromatography (15% EtOAc/hexane, R_f = 0.20) to afford **3-34b** (162 mg, 71%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 - 7.45 (m, 2H), 6.86 - 6.89 (m, 2H), 6.82 (t, *J* = 2.6 Hz, 1H), 5.28 (d, *J* = 2.5 Hz, 1H), 4.51 (d, *J* = 2.5 Hz, 1H), 3.84 - 3.97 (m, 2H), 3.81 (s, 3H), 3.71 (s, 3H), 2.50 (dd, *J* = 9.3, 2.6 Hz, 1H), 2.30 (dd, *J* = 9.3, 2.6 Hz, 1H), 1.41 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 188.7, 170.1, 159.5, 156.8, 128.9, 128.7 (2C), 120.2, 119.9, 114.0 (2C), 91.9, 64.0, 55.3, 52.3, 34.7, 17.3, 14.4. **IR:** 2982.4 (w), 2954.7 (w), 2840.0 (w), 1797.8 (w), 1730.1 (s), 1606.9 (m), 1512.0 (s), 1247.8 (s), 1174.2 (s), 1109.3 (s), 1024.9 (s). **HRMS** (EI) *m/z*: [M-H+] calcd. for $C_{18}H_{20}O_5$, 316.1311; found, 316.1319.

c. Reaction optimizations

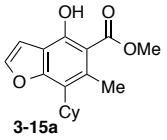
Procedure for Catalyst Screening: To a flask charged with a stir bar, 4 Å molecular sieves (approx. 0.6 g) and an appropriate loading of the relevant Lewis acid was added a solution of alkylidene cyclopropane **3-10a** (1.0 equiv) in CH_2Cl_2 (0.1 M) at room temperature. The reaction mixture was either kept at room temperature or refluxed. Upon complete disappearance of cyclopropane **3-10a** on TLC, the reaction was quenched with water. The mixture was extracted with CH_2Cl_2, dried with Na_2SO_4, and purification via column chromatography provided the *o*-phenolic ester product.

Procedure for Optimization of Catalyst Loading: To a flask charged with a stir bar, 4 Å molecular sieves (approx. 0.6 g), and the appropriate $Yb(OTf)_3$ loading (20, 15 or 10 mol%) was added a solution of alkylidene cyclopropane **3-10a** (1.0 equiv.) in CH_2Cl_2 (0.1 M) at room temperature and then the mixture was heated to reflux. Upon complete disappearance of cyclopropane **3-10a** on TLC, the reaction was quenched with water. The mixture was extracted with CH_2Cl_2, dried with Na_2SO_4, and purification via column chromatography provided the *o*-phenolic ester product.

Procedure for Solvent Screening: To a flask charged with a stir bar, 4 Å molecular sieves (approx. 0.6 g), and 15 mol% Yb(OTf)3 was added a solution of alkylidene cyclopropane **3-10a** (1.0 equiv) in the appropriate solvent (PhMe, 1,2-DCE, or MeCN) (0.1 M) at room temperature. The reaction mixture was heated to the indicated temperature and upon complete disappearance of cyclopropane **3-10a** on TLC, the reaction was quenched with water. The mixture was extracted with CH_2Cl_2, dried with Na_2SO_4, and purification via column chromatography provided the *o*-phenolic ester product.

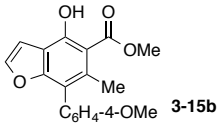
d. Catalytic formal homo-Nazarov-type cyclizations

General Procedure: A solution of the corresponding cyclopropane (0.1 M in CH_2Cl_2 or 1,2-DCE) was added to a dried round bottom flask containing $Yb(OTf)_3$ and 4 Å molecular sieves (1-2 mm beads, 0.6-0.8 g). The reaction was heated to reflux and monitored via TLC. Upon complete disappearance of the starting material, the reaction was quenched with water. The mixture was extracted with CH_2Cl_2, dried with Na_2SO_4, and purification via column chromatography provided the *o*-phenolic ester product.



3-15a

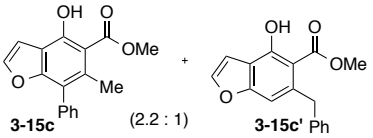
Methyl 7-cyclohexyl-4-hydroxy-6-methylbenzofuran-5-carboxylate (3-15a). According to the general procedure, $Yb(OTf)_3$ (24.1 mg, $3.89*10^{-2}$ mmol), cyclopropane **3-10a** (75.1 mg, 0.260 mmol), and CH_2Cl_2 (2.6 mL) were mixed and refluxed for 12 hrs to afford **3-15a** (68.0 mg, 91%) after purification via flash chromatography (5% Et_2O/hexane, R_f = 0.30) as a white solid (mp: 140-142 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.28 (s, 1H), 7.51 (d, J = 2.1 Hz, 1H), 6.88 - 6.91 (d, J = 2.1 Hz, 1H), 3.97 (s, 3H), 2.98 - 3.06 (m, 1H), 2.55 (s, 3H), 2.07 - 2.18 (m, 2H), 1.84 - 1.90 (m, 2H), 1.75 - 1.80 (m, 1H), 1.66 (d, J = 12.8 Hz, 2H), 1.36 - 1.46 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.7, 157.8, 155.3, 143.0, 132.8, 123.4, 115.6, 107.8, 104.4, 52.0, 39.0, 30.9 (2C), 27.4 (2C), 26.1, 18.6. **IR:** 2941.9 (m), 2928.5 (m), 2854.1 (m), 1663.9 (m), 1432.7 (m), 1300.7 (s), 1290.2 (s), 1203.6 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{17}H_{20}O_4$, 288.1362; found, 288.1367.



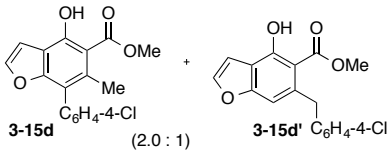
3-15b

Methyl 4-hydroxy-7-(4-methoxyphenyl)-6-methylbenzofuran-5-carboxylate (3-15b). According to the general procedure, $Yb(OTf)_3$ (21.6 mg, $3.48*10^{-2}$ mmol), cyclopropane **3-10b** (72.0 mg, 0.231 mmol), and CH_2Cl_2 (2.3 mL) were mixed and refluxed for 5 hrs to afford **3-15b** (38.2 mg, 53%) after purification via flash chromatography (5% Et_2O/hexane, R_f = 0.15) as a white solid (mp: 130-131 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.99 (s, 1H), 7.46 (d, J = 2.1 Hz, 1H), 7.24 - 7.28 (m, 2H), 7.00 - 7.04 (m, 2H), 6.96 (d, J = 2.1 Hz, 1H),

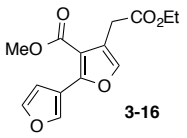
3.99 (s, 3H), 3.88 (s, 3H), 2.44 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.0, 158.9, 157.3, 157.3, 144.0, 134.8, 131.7 (2C), 127.7, 119.8, 114.8, 113.8 (2C), 107.2, 104.9, 55.2, 52.1, 20.3. **IR:** 3121.4 (w), 3000.2 (w), 2953.6 (w), 2835.2 (w), 1726.6 (m), 1654.9 (m), 1512.5 (m), 1224.1 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{18}H_{16}O_5$, 312.0998; found, 312.1003.



Methyl 4-hydroxy-6-methyl-7-phenylbenzofuran-5-carboxylate (3-15c, major) and methyl 6-benzyl-4-hydroxybenzofuran-5-carboxylate (3-15c', minor). According to the general procedure, $Yb(OTf)_3$ (24.1 mg, $3.89*10^{-2}$ mmol), cyclopropane **3-10c** (73.6 mg, 0.261 mmol), and CH_2Cl_2 (2.6 mL) were mixed and refluxed for 24 hrs to afford a 2.2:1 mixture of **3-15c** and **3-15c'** (52.0 mg, 71%) after purification via flash chromatography (5% Et_2O/hexane, R_f = 0.28) as a white solid (mp: 118-120 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.11 (s, 0.45, minor), 12.01 (s, 1H, major), 7.53 (d, *J* = 2.1 Hz, 0.45, minor), 7.46 - 7.51 (m, 2H, major), 7.46 (d, *J* = 2.1 Hz, 1H, major), 7.40 - 7.44 (m, 1H, major), 7.32 - 7.35 (m, 2H, major), 7.24 - 7.29 (m, 0.90, minor), 7.15 - 7.20 (m, 0.45, minor), 7.05 - 7.09 (m, 0.90, minor), 6.97 (d, *J* = 2.1 Hz, 1H, major), 6.95 - 6.96 (m, 0.45, minor), 6.89 (s, 0.45, minor), 4.39 (s, 0.90, minor), 4.00 (s, 3H, major), 3.79 (s, 1.35, minor), 2.43 (s, 3H, major). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.0, 172.3, 159.0, 158.4, 157.5, 157.1, 144.0, 141.3, 139.6, 135.7, 134.6, 130.6, 128.4, 128.3, 127.5, 125.9, 120.1, 115.9, 114.9, 107.8, 107.2, 106.0, 104.9, 52.1, 51.8, 42.6, 20.4. **IR:** 3058.2 (w), 3003.3 (w), 2953.1 (w), 1726.6 (s), 1655.2 (m), 1437.4 (s), 1293.9 (s), 1223.1 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{18}H_{16}O_5$, 282.0892; found, 282.0896.

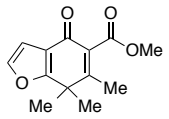


Methyl 7-(4-chlorophenyl)-4-hydroxy-6-methylbenzofuran-5-carboxylate (3-15d) and methyl 6-(4-chlorobenzyl)-4-hydroxybenzofuran-5-carboxylate (3-15d'). According to the general procedure B, $Yb(OTf)_3$ (22.8 mg, $3.68*10^{-2}$ mmol), cyclopropane **3-10d** (74.3 mg, 0.235 mmol), and 1,2-DCE (2.4 mL) were mixed and refluxed for 3 hrs to afford a 2.0:1 mixture of **3-15d** and **3-15d'** (39.4 mg, 53%) after purification via flash chromatography (2% Et_2O/hexane, R_f = 0.12) as a white solid (mp: 118-120 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.14 (s, 0.51, minor), 12.07 (s, 1H, major), 7.57 (d, J = 2.1 Hz, 0.51, minor), 7.46 - 7.50 (m, 3H, major), 7.28 - 7.32 (m, 2H, major), 7.25 (d, J = 8.5 Hz, 1.02, minor), 7.02 (d, J = 8.5 Hz, 1.02, minor), 7.00 (d, J = 2.1 Hz, 1H, major), 6.98 - 6.99 (m, 0.51, minor), 6.91 (s, 0.51, minor), 4.37 (s, 1.02, minor), 4.02 (s, 3H, major), 3.82 (s, 1.53, minor), 2.45 (s, 3H, major). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.9, 172.0, 159.1, 158.3, 157.7, 156.9, 144.2, 144.0, 139.9, 138.8, 134.7, 134.0, 133.5, 132.0, 131.6, 129.5, 128.6, 128.4, 118.8, 116.1, 115.0, 107.8, 107.3, 105.9, 105.0, 104.9, 52.2, 51.9, 42.0, 20.3. **IR:** 3126.7 (w), 2953.0 (w), 1728.4 (w), 1656.2 (s), 1437.5 (s), 1294.0 (s), 1222.7 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{17}H_{13}O_4Cl$, 316.0502; found, 316.0495.



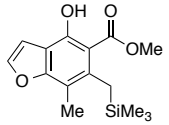
Methyl 4-(2-ethoxy-2-oxoethyl)-[2,3'-bifuran]-3-carboxylate (3-16). According to the general procedure, $Yb(OTf)_3$ (23.4 mg, $3.77*10^{-2}$ mmol), cyclopropane **3-10e** (70.0 mg,

0.252 mmol), and CH_2Cl_2 (2.5 mL) were mixed and refluxed for 20 hrs to afford **3-16** (48.5 mg, 69%) after purification via flash chromatography (20% Et_2O/hexane, R_f = 0.23) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.34 - 8.39 (m, 1H), 7.43 (t, *J* = 1.7 Hz, 1H), 7.33 (s, 1H), 6.91 (dd, *J* = 1.7, 0.9 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 3.81 (s, 3H), 3.64 (s, 2H), 1.26 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.0, 164.0, 153.2, 143.8, 142.6, 139.6, 119.3, 116.5, 112.0, 109.2, 60.8, 51.1, 30.9, 14.2. **IR:** 2984.6 (w), 2955.1 (w), 1714.0 (s), 1439.0 (m), 1160.4 (s), 1083.0 (s), 1020.6 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{14}H_{14}O_6$, 278.0790; found, 278.0778.



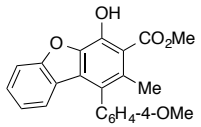
3-18

Methyl 6,7,7-trimethyl-4-oxo-4,7-dihydrobenzofuran-5-carboxylate (3-18). According to the general procedure, $Yb(OTf)_3$ (29.5 mg, 4.76*10^{-2} mmol), cyclopropane **3-10f** (76.4 mg, 0.326 mmol), and CH_2Cl_2 (3.2 mL) were mixed and refluxed for 5 hrs to afford **3-18** (48.3 mg, 63%) after purification via flash chromatography (30% Et_2O/hexane, R_f = 0.14) as a light brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 2.1 Hz, 1H), 6.71 (d, *J* = 2.1 Hz, 1H), 3.87 (s, 3H), 2.03 (s,3 H), 1.48 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 178.4, 170.0, 167.7, 156.5, 143.0, 133.2, 117.6, 106.1, 52.3, 39.4, 24.7 (2C), 15.3. **IR:** 3125.4 (w), 3981.2 (w), 2952.0 (w), 1731.5 (s), 1655.5 (s), 1471.8 (m), 1168.9 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{13}H_{14}O_4$, 234.0892; found, 234.0891.



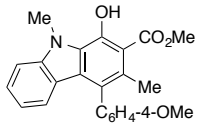
3-19

Methyl 4-hydroxy-7-methyl-6-((trimethylsilyl)methyl)benzofuran-5-carboxylate (3-19). According to the general procedure, $Yb(OTf)_3$ (22.4 mg, $3.61*10^{-2}$ mmol), cyclopropane **3-10g** (74.8 mg, 0.256 mmol), and CH_2Cl_2 (2.5 mL) were mixed and refluxed for 5 hrs to afford **3-19** (51.1 mg, 68%) after purification via flash chromatography (5% Et_2O/hexane, R_f = 0.26) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.10 (s, 1H), 7.40 (d, J = 2.1 Hz, 1H), 6.82 (d, J = 2.1 Hz, 1H), 3.83 (s, 3H), 2.71 (s, 2H), 2.19 (s, 3H), 0.26 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.9, 163.8, 157.8, 140.8, 136.3, 135.2, 121.1, 108.9, 93.2, 51.2, 26.8, 18.1, 0.4. **IR:** 2952.7 (m), 2893.3 (w), 1743.3 (w), 1639.3 (m), 1607.3 (m), 1232.6 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{15}H_{20}O_4Si$, 292.1131; found, 292.1135.



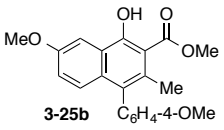
3-21b

Methyl 4-hydroxy-1-(4-methoxyphenyl)-2-methyldibenzo[*b*,*d*]furan-3-carboxylate (3-21b). According to the general procedure, $Yb(OTf)_3$ (20.0 mg, $3.22*10^{-2}$ mmol), cyclopropane **3-20b** (74.8 mg, 0.206 mmol), and CH_2Cl_2 (2.0 mL) were mixed and refluxed for 4 hrs to afford **3-21b** (58.4 mg, 78%) after purification via flash chromatography (5% Et_2O/hexane, R_f = 0.14) as a white solid (mp: 173-175 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.16 (s, 1H), 8.18 - 8.23 (m, 1H), 7.44 - 7.47 (m, 1H), 7.34 - 7.40 (m, 2H), 7.28 - 7.32 (m, 2H), 7.04 - 7.08 (m, 2H), 4.01 (s, 3H), 3.91 (s, 3H), 2.48 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.8, 159.0, 158.8, 158.4, 155.6, 138.6, 131.9 (2C), 127.6, 126.2, 123.6, 123.4, 122.8, 119.7, 113.9 (2C), 111.3, 110.7, 107.7, 55.3, 52.2, 20.8. **IR:** 3004.1 (w), 2959.3 (w), 2926.1 (w), 2837.8 (w), 1655.3 (m), 1608.0 (m), 1480.1 (m), 1208.7 (s), 1011.9 (s), 799.5 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{22}H_{18}O_5$, 362.1154; found, 362.1165.



3-23b

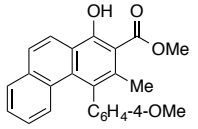
Methyl 1-hydroxy-4-(4-methoxyphenyl)-3,9-dimethyl-9*H*-carbazole-2-carboxylate (3-23b). According to the general procedure, $Yb(OTf)_3$ (29.8 mg, $4.80*10^{-2}$ mmol), cyclopropane **3-22b** (114.1 mg, 0.304 mmol), and CH_2Cl_2 (3.0 mL) were mixed and refluxed for 6 hrs to afford **3-23b** (79.2 mg, 69%) after purification via preparatory TLC (5% Et_2O/hexane, R_f = 0.21) as a yellow solid (mp: 174-176 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.05 (s, 1H), 7.34 - 7.43 (m, 2H), 7.18 - 7.24 (m, 2H), 7.05 - 7.11 (m, 2H), 6.88 (ddd, *J* = 7.9, 6.8, 0.9 Hz, 1H), 6.59 (d, *J* = 7.9 Hz, 1H), 4.25 (s, 3H), 4.01 (s, 3H), 3.95 (s, 3H), 2.36 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.7, 158.8, 150.7, 142.8, 133.0, 131.1 (2C), 128.4, 127.5, 127.0, 126.8, 126.4, 123.0, 122.3, 118.8, 114.3 (2C), 108.7, 108.7, 55.3, 52.1, 32.1, 19.7. **IR:** 2998.0 (w), 2951.4 (w), 2834.6 (w), 1654.0 (m), 1440.0 (s), 1321.6 (s), 1241.5 (s), 1149.0 (s), 1038.4 (m). **HRMS** (ESI) *m/z*: [M-H$^+$] calcd. for $C_{23}H_{22}O_4N$, 376.1543; found, 376.1535.



3-25b

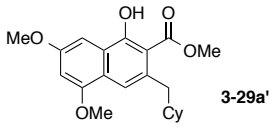
Methyl 1-hydroxy-7-methoxy-4-(4-methoxyphenyl)-3-methyl-2-naphthoate (3-25b). According to the general procedure B, $Yb(OTf)_3$ (30.1 mg, $4.85*10^{-2}$ mmol), cyclopropane **3-24b** (109.0 mg, 0.309 mmol), and CH_2Cl_2 (3.1 mL) were mixed and refluxed for 16.5 hrs to afford **3-25b** (84.3 mg, 77%) after purification via flash chromatography (5% Et_2O/hexane, R_f = 0.11) as a yellow solid (mp: 140-142 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ

12.42 (s, 1H), 7.73 (d, J = 2.7 Hz, 1H), 7.16 (d, J = 9.2 Hz, 1H), 7.10 - 7.13 (m, 2H), 7.08 (dd, J = 9.2, 2.7 Hz, 1H), 6.99 - 7.04 (m, 2H), 4.01 (s, 3H), 3.95 (s, 3H), 3.90 (s, 3H), 2.31 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.4, 159.8, 158.5, 157.0, 132.3, 131.8 (2C), 131.7, 130.8, 129.8, 128.0, 124.2, 121.6, 113.8 (2C), 107.3, 101.9, 55.4, 55.2, 52.2, 20.9. **IR:** 2998.2 (w), 2952.3 (w), 2834.8 (w), 1732.5 (w), 1646.3 (m), 1580.1 (m), 1513.5 (s), 1436.8 (m), 1326.6 (m), 1219.0 (s), 1034.0 (m), 829.9 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{21}H_{20}O_5$, 352.1311; found, 352.1307.



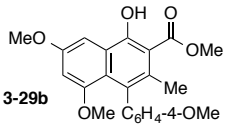
3-27b

Methyl 1-hydroxy-4-(4-methoxyphenyl)-3-methylphenanthrene-2-carboxylate (3-27b). According to the general procedure, $Yb(OTf)_3$ (21.0 mg, $3.39*10^{-2}$ mmol), cyclopropane **3-26b** (80.6 mg, 0.216 mmol), and CH_2Cl_2 (2.2 mL) were mixed and refluxed for 3 hrs to afford **3-27b** (35.8 mg, 44%) after purification via flash chromatography (10% Et_2O/hexane, R_f = 0.32) as a yellow solid (mp: 141-143 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.98 (s, 1H), 8.41 (d, J = 8.9 Hz, 1H), 7.77 - 7.84 (m, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.46 (d, J = 8.9 Hz, 1H), 7.40 - 7.44 (m, 1H), 7.10 - 7.17 (m, 2H), 7.00 - 7.10 (m, 3H), 4.02 (s, 3H), 3.92 (s, 3H), 2.33 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.8, 159.1, 158.7, 135.9, 135.2, 135.0, 133.8, 131.7 (2C), 131.3, 130.1, 128.9, 128.4, 126.7, 126.7, 124.8, 122.2, 120.8, 114.7 (2C), 109.0, 55.3, 52.3, 21.6. **IR:** 3053.5 (w), 2952.4 (w), 2835.5 (w), 1734.1 (w), 1649.6 (m), 1607.1 (m), 1589.8 (m), 1438.8 (m), 1335.3 (m), 1235.6 (s), 1166.7 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{24}H_{20}O_4$, 372.1362; found, 372.1360.



3-29a'

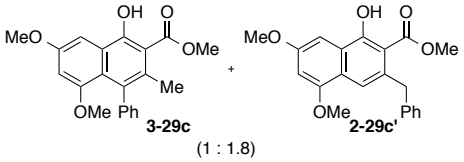
Methyl 3-(cyclohexylmethyl)-1-hydroxy-5,7-dimethoxy-2-naphthoate (3-29a'). According to the general procedure, $Yb(OTf)_3$ (19.2 mg, $3.10*10^{-2}$ mmol), cyclopropane **3-28a** (74.8 mg, 0.209 mmol), and 1,2-DCE (2.1 mL) were mixed and refluxed for 3 hrs to afford **3-29a'** (29.4 mg, 39%) after purification via flash chromatography (5% Et_2O/hexane, R_f = 0.26) as a light yellow solid (mp: 135-137 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.45 (s, 1H), 7.35 (s, 1H), 7.23 (d, *J* = 2.1 Hz, 1H), 6.59 (d, *J* = 2.1 Hz, 1H), 3.99 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H), 2.89 (d, *J* = 6.7 Hz, 2H), 1.56 - 1.71 (m, 5H), 1.35 - 1.45 (m, 1H), 1.11 - 1.18 (m, 3H), 0.99 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.2, 160.8, 157.7, 155.7, 134.8, 124.9, 123.6, 115.5, 107.0, 100.9, 93.8, 55.7, 55.5, 52.1, 45.0, 39.9, 33.5 (2C), 26.6, 26.4 (2C). **IR:** 2995.1 (w), 2924.7 (m), 2843.5 (m), 1642.8 (m), 1600.7 (m), 1583.9 (m), 1433.9 (s), 1340.5 (m), 1247.4 (s), 1194.0 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{21}H_{26}O_5$, 358.1780; found, 358.1779.



3-29b

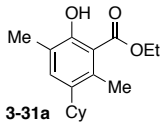
Methyl 1-hydroxy-5,7-dimethoxy-4-(4-methoxyphenyl)-3-methyl-2-naphthoate (3-29b). According to the general procedure, $Yb(OTf)_3$ (27.5 mg, $4.43*10^{-2}$ mmol), cyclopropane **3-28b** (110.0 mg, 0.288 mmol), and CH_2Cl_2 (2.9 mL) were mixed and refluxed for 3 hrs to afford **3-29b** (88.3 mg, 80%) after purification via flash chromatography (10% Et_2O/hexane, R_f = 0.18) as a yellow solid (mp: 153-155 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.11 (s, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 6.99 - 7.04 (m, 2H), 6.87 - 6.92 (m, 2H), 6.51 (d, *J* = 2.4 Hz, 1H),

3.99 (s, 3H), 3.94 (s, 3H), 3.88 (s, 3H), 3.33 (s, 3H), 2.19 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.2, 158.9, 157.5, 157.5, 157.5, 136.6, 130.2 (3C), 129.1, 125.7, 123.4, 112.6 (2C), 108.1, 102.9, 94.5, 55.8, 55.4, 55.3, 52.2, 20.6. **IR:** 3048.0 (w), 2952.9 (w), 2380.0 (w), 1649.5 (m), 1584.1 (m), 1512.2 (m), 1439.8 (m), 1327.2 (m), 1209.3 (s), 1062.9 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{22}H_{22}O_6$, 382.1416; found, 382.1399.



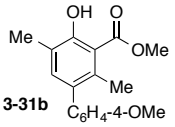
Methyl 1-hydroxy-5,7-dimethoxy-3-methyl-4-phenyl-2-naphthoate (3-29c, minor) and methyl 3-benzyl-1-hydroxy-5,7-dimethoxy-2-naphthoate (3-29c', major). According to the general procedure, $Yb(OTf)_3$ (20.8 mg, $3.35*10^{-2}$ mmol), cyclopropane **3-28c** (66.2 mg, 0.188 mmol), and CH_2Cl_2 (2.1 mL) were mixed and refluxed for 18.5 hrs to afford a mixture of **3-29c** and **3-29c'** (64.9 mg, 98%) after purification via flash chromatography (5% Et_2O/hexane, R_f = 0.19) as a yellow solid (mp: 119-121 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.50 (s, 1H, major), 12.17 (s, 0.57, minor), 7.54 (s, 1H, major), 7.40 (d, *J* = 2.4 Hz, 0.57, minor), 7.32 - 7.38 (m, 1.14, minor), 7.29 - 7.31 (m, 0.57, minor), 7.28 (d, *J*=2.4 Hz, 1H, major), 7.21 - 7.25 (m, 2H, major), 7.11 - 7.17 (m, 2.14, major + minor), 7.06 (d, *J* = 7.0 Hz, 2H, major), 6.64 (d, *J* = 2.4 Hz, 1H, major), 6.51 (d, *J* = 2.4 Hz, 0.57, minor), 4.41 (s, 2H, major), 3.99 (s, 1.71, minor), 3.94 - 3.97 (m, 7.71, major + minor), 3.76 (s, 3H, major), 3.29 (s, 1.71, minor), 2.19 (s, 1.71, minor). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.2, 172.6, 161.1, 159.0, 158.1, 157.5, 157.3, 155.8, 144.3, 142.1, 133.3, 129.8, 129.5, 129.3, 128.1, 128.0, 127.1, 125.7, 125.5, 125.4, 123.7, 123.0, 116.4, 108.0, 107.0, 102.8, 101.0, 94.5, 93.9, 55.6, 55.6, 55.5, 55.4, 52.2, 51.8, 42.9, 20.5. **IR:** 3003.4 (w), 2952.5 (w), 2853.1 (w), 1727.6 (m),

1649.9 (s), 1437.6 (m), 1331.1 (m), 1283.1 (s), 1248.0 (s), 1166.8 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{21}H_{20}O_5$, 352.1311; found, 352.1318.



3-31a

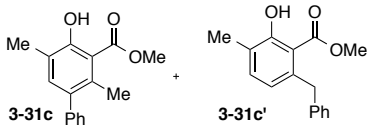
Ethyl 3-cyclohexyl-6-hydroxy-2,5-dimethylbenzoate (3-31a). According to the general procedure, $Yb(OTf)_3$ (38.8 mg, $6.26*10^{-2}$ mmol), cyclopropane **3-30a** (60.0 mg, 0.217 mmol), and CH_2Cl_2 (2.2 mL) were mixed and refluxed for 23 hrs to afford **3-31a** (39.4 mg, 66%) after purification via flash chromatography (2% Et_2O/hexane, R_f = 0.12) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.62 (s, 1H), 7.16 (s, 1H), 4.43 (q, J = 7.3 Hz, 2H), 2.68 - 2.77 (m, 1H), 2.45 (s, 3H), 2.23 (s, 3H), 1.71 - 1.90 (m, 5H), 1.24 - 1.47 (m, 8H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.0, 157.3, 137.0, 134.2, 132.7, 123.4, 113.4, 61.5, 39.6, 34.0 (2C), 27.2 (2C), 26.3, 17.4, 16.0, 14.2. **IR:** 2980.1 (w), 2924.7 (m), 2850.5 (m), 1653.0 (s), 1446.6 (m), 1320.0 (s), 1260.3 (s), 1093.4 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{17}H_{24}O_3$, 276.1725; found, 276.1723.



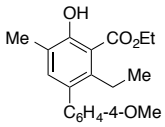
3-31b

Methyl 4-hydroxy-4'-methoxy-2,5-dimethyl-[1,1'-biphenyl]-3-carboxylate (3-31b). According to the general procedure, $Yb(OTf)_3$ (26.5 mg, $4.27*10^{-2}$ mmol), cyclopropane **3-30b** (72.0 mg, 0.251 mmol), and CH_2Cl_2 (2.5 mL) were mixed and refluxed for 23 hrs to afford **3-31b** (35.3 mg, 49%) after purification via flash chromatography (5% Et_2O/hexane, R_f = 0.19) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.21 (s, 1H), 7.14 - 7.18 (m,

3H), 6.91 - 6.96 (m, 2H), 3.98 (s, 3H), 3.85 (s, 3H), 2.36 (s, 3H), 2.26 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.7, 159.6, 158.4, 137.2, 135.1, 134.4, 133.9, 130.8 (2C), 123.6, 113.5 (2C), 112.6, 55.3, 52.1, 20.5, 15.8. **IR:** 2997.9 (w), 2952.8 (w), 2853.5 (w), 1655.4 (m), 1608.3 (m), 1512.8 (m), 1435.4 (m), 1233.5 (s), 1174.3 (s), 1053.6 (s), 802.9 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{17}H_{18}O_4$, 286.1205; found, 286.1213.

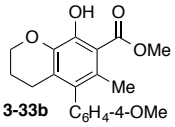


Methyl 4-hydroxy-2,5-dimethyl-[1,1'-biphenyl]-3-carboxylate (3-31c, major) and methyl 6-benzyl-2-hydroxy-3-methylbenzoate (3-31c', minor). According to the general procedure, $Yb(OTf)_3$ (41.8 mg, $6.74*10^{-2}$ mmol), cyclopropane **3-30c** (120.0 mg, 0.468 mmol), and 1,2-DCE (4.6 mL) were mixed and refluxed for 5.5 hrs to afford a 2.7:1 mixture of **3-31c** and **3-31c'** (70.6 mg, 59%) after purification via flash chromatography (2% Et_2O/hexane, R_f = 0.12) as a white solid (mp: 60-62 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.50 (s, 0.37, minor), 11.32 (s, 1H, major), 7.42 - 7.46 (m, 2H, major), 7.35 - 7.39 (m, 1H, major), 7.27 - 7.31 (m, 3.11, major + minor), 7.23 (s, 1H, major), 7.18 - 7.22 (m, 0.37, minor), 7.09 (dd, *J* = 7.9, 0.9 Hz, 0.74, minor), 6.69 (d, *J* = 7.6 Hz, 0.37, minor), 4.32 (s, 0.74, minor), 4.02 (s, 3H, major), 3.80 (s, 1.11, minor), 2.41 (s, 3H, major), 2.29 - 2.33 (m, 4.11, major + minor). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.6, 172.0, 161.2, 159.8, 142.0, 141.5, 140.0, 136.9, 135.0, 135.0, 134.3, 129.7, 128.2, 128.1, 128.0, 126.6, 125.7, 125.2, 123.7, 122.8, 112.6, 111.5, 52.1, 51.8, 42.0, 20.5, 15.9, 15.7. **IR:** 3027.0 (w), 2951.6 (w), 1656.2 (s), 1611.1 (m), 1584.2 (m), 1434.4 (s), 1335.2 (s), 1195.1 (s), 992.0 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{16}H_{16}O_3$, 256.1099; found, 256.1111.



3-31h

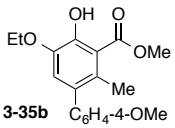
Ethyl 2-ethyl-4-hydroxy-4'-methoxy-5-methyl-[1,1'-biphenyl]-3-carboxylate (3-31h). According to the general procedure, $Yb(OTf)_3$ (22.1 mg, $3.56*10^{-2}$ mmol), cyclopropane **3-30h** (63.4 mg, 0.202 mmol), and CH_2Cl_2 (2.0 mL) were mixed and refluxed for 2.5 hrs to afford **3-31h** (36.8 mg, 58%) after purification via flash chromatography (15% Et_2O/hexane, R_f = 0.50) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.18 (s, 1H), 7.13 - 7.18 (m, 2H), 7.11 (s, 1H), 6.90 - 6.95 (m, 2H), 4.47 (q, J = 7.3 Hz, 2H), 3.86 (s, 3H), 2.85 (q, J = 7.3 Hz, 2H), 2.24 (s, 3H), 1.44 (t, J = 7.3 Hz, 3H), 1.00 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.0, 159.6, 158.4, 141.7, 137.4, 134.5, 133.7, 130.6 (2C), 123.5, 113.3 (2C), 111.9, 61.7, 55.2, 24.9, 16.3, 15.8, 13.9. **IR:** 2978.8 (w), 2932.7 (w), 2835.4 (w), 1651.5 (m), 1608.6 (m), 1512.4 (m), 1457.0 (m), 1371.3 (m), 1284.3 (s), 1226.4 (s), 1082.8 (m), 869.6 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{19}H_{22}O_4$, 314.1518; found, 314.1528.



3-33b

Methyl 8-hydroxy-5-(4-methoxyphenyl)-6-methylchromane-7-carboxylate (3-33b). According to the general procedure, $Yb(OTf)_3$ (32.5 mg, $5.24*10^{-2}$ mmol), cyclopropane **3-32b** (102.0 mg, 0.311 mmol), and 1,2-DCE (3.0 mL) were mixed and refluxed for 2.5 hrs to afford **3-33b** (26.3 mg, 26%) after purification via flash chromatography (20% EtOAc/hexane, R_f = 0.24) as a yellow solid (mp: 115-117 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.39 (s, 1H), 6.97 - 7.06 (m, 2H), 6.92 - 6.96 (m, 2H), 4.18 - 4.23 (m, 2H), 3.94 (s, 3H),

3.85 (s, 3H), 2.28 (t, J = 6.4 Hz, 2H), 2.08 (s, 3H), 1.84 - 1.93 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.9, 158.4, 149.3, 141.4, 133.5, 132.2, 130.7 (2C), 127.9, 126.5, 113.9 (2C), 112.2, 66.1, 55.2, 52.1, 24.8, 22.1, 19.5. **IR:** 3427.9 (w), 2951.3 (w), 2873.6 (w), 2836.7 (w), 1727.0 (m), 1655.3 (m), 1608.0 (m), 1513.0 (m), 1422.4 (m), 1333.1 (m), 1224.4 (s), 1066.1 (s). **HRMS** (ESI) *m/z*: [M-Na$^+$] calcd. for $C_{19}H_{20}O_5Na$, 351.1203; found, 351.1195.



Methyl 5-ethoxy-4-hydroxy-4'-methoxy-2-methyl-[1,1'-biphenyl]-3-carboxylate (3-35b). According to the general procedure, $Yb(OTf)_3$ (18.1 mg, 2.92*10^{-2} mmol), cyclopropane **3-34b** (58.5 mg, 0.185 mmol), and 1,2-DCE (1.8 mL) were mixed and refluxed for 2.5 hrs to afford **3-35b** (30.1 mg, 51%) after purification via flash chromatography (15% EtOAc/hexane, R_f = 0.22) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.72 (s, 1H), 7.15 - 7.20 (m, 2H), 6.92 - 6.96 (m, 2H), 6.86 (s, 1H), 4.08 (q, J = 7.0 Hz, 2H), 3.97 (s, 3H), 3.85 (s, 3H), 2.25 (s, 3H), 1.45 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.4, 158.5, 149.2, 144.7, 134.3, 133.6, 130.7 (2C), 127.7, 118.1, 115.7, 113.5 (2C), 64.7, 55.3, 52.3, 19.2, 14.8. **IR:** 3414.3 (w), 2953.7 (w), 2930.6 (w), 2839.7 (w), 1728.7 (m), 1438.6 (m), 1242.0 (s), 1175.4 (s), 1062.0 (s). **HRMS** (EI) *m/z*: [M$^+$] calcd. for $C_{18}H_{20}O_5$, 316.1311; found, 316.1298

3.5 References

1. For recent reviews on the reactivity and synthesis of alkylidene cyclopropanes see: a) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2014**, *114*, 7317-7420; b) Pellissier, H. *Tetrahedron* **2010**, *66*, 8341.
2. Johnson, W. T. G.; Borden, W. T. *J. Am. Chem. Soc.* **1997**, *119*, 5930-5933.
3. Fujino, D.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2011**, *133*, 9682.
4. Hu, B.; Xing, S.; Wang, Z. *Org. Lett.* **2008**, *10*, 5481.
5. Tang, X.-Y.; Shi, M. *Eur. J. Org. Chem.* **2010**, 4106-4110.
6. Aponte-Guzmán, J.; Taylor, J. E., Jr.; Tillman, E.; France, S. *Org. Lett.* **2014**, *16*, 3788.
7. a) Phun, L. H.; Patil, D. V.; Cavitt, M. A. *Org. Lett*. **2011**, *13*, 1952; b) Patil, D. V.; Cavitt, M. A.; Grzybowski, P.; France, S. *Chem. Comm.* **2011**, *47*, 10278; c) Phun, L. H.; Aponte-Guzman, J.; France, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3198; d) Martin, M. C.; Patil, D. V.; France, S. *J. Org. Chem.* **2014**, *79*, 3030; h) Cavitt, M. C.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804.
8. For applications of o-phenolic esters and naphthols see: Panda, N.; Mothkuri, R.; Pal, A.; Paital, A. *Adv. Synth. Catal.* **2013**, *355*, 2809.
9. For a review on recent synthetic approaches to alkylidene cyclopropanes, see: Audran, G.; Pellissier, H. *Adv. Synth. Catal.* **2010**, *352*, 575.
10. Ullman, E. F.; Fanshawe, W. J. *J. Am. Chem. Soc.* **1961**, *83*, 2379.
11. For representative examples of the formation of alkylidene cyclopropanes from Rh(II)-catalyzed cyclopropanation of allenes and α-diazocompounds, see: a) Cheng, C.; Shimo, T.; Domekawa, K.; Baba, M. *Tetrahedron* **1998**, *54*, 2031; b) Huval, C.

C.; Singleton, D. A. *J. Org. Chem.* **1994**, *59*, 2020; c) Gregg, T. M.; Farrugia, M. K.; Frost, J. R. *Org. Lett.* **2009**, *11*, 4434.

12. Conversions were determined by both TLC and ^{1}H NMR for the consumption of ACP **10a**. See Experimental Information.

13. Changing the solvent (i.e., CH_3CN, 1,2-DCE, toluene) afforded reduced yields or poor conversion. See Experimental Information.

14. We also examined $Al(OTf)_3$ as the catalyst (higher selectivity), but it proved to be less effective for the substrate scope studies.

15. Hanna, S. Y.; Khalil, S. M.; Shandala, M. Y. Z. *Naturforsch., A* **2004**, *59*, 971.

16. Wang reported the formation of an alkylidene-2,3-dihydrofuran that is similar to intermediate **16** from a benzylidene cyclopropane 1,1-ketoester (see ref 4). For representative examples of the formation of 2,3-dihydrofurans from donor−acceptor cyclopropanes, see: a) Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2001**, *3*, 2717; b) Bowman, R. K.; Johnson, J. S. *Org. Lett.* **2006**, *8*, 573; c) Schneider, T. F.; Kaschel, J.; Dittrich, B.; Werz, D. B. *Org. Lett.* **2009**, *11*, 2317.

17. Schotes, C.; Mezzetti, A. *ACS Catal.* **2012**, *2*, 528.

18. Duttwyler, S.; Zhang, Y.; Linden, A.; Reed, C. A.; Baldridge, K. K.; Siegel, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3787.

19. For representative examples of Hiyama coupling reactions: a) Hiyama, T. J. *Organomet. Chem.* **2002**, *653*, 58; b) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2202.

20. For the seminal contribution by Fleming (Fleming oxidation), see: Fleming, I.; Sanderson, P. E. J. *Tetrahedron Lett.* **1987**, *28*, 4229.

21. For examples of heteroaryl π-nucleophiles in the formal homo-Nazarov reaction, see: a) Greiner-Bechert, L.; Sprang, T.; Otto, H.-H. *Monatsh. Chem.* **2005**, *136*, 635; b) Yadav, V. K.; Kumar, N. V. *Chem. Commun.* **2008**, 3774; c) De Simone, F.; Andres, J.; Torosantucci, R.; Waser, *J. Org. Lett.* **2009**, *11*, 1023.

22. For formal homo-Nazarov literature using an aryl group as π-nucleophiles: a) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 271; b) Yoshida, E.; Nishida, K.; Toriyabe, K.; Taguchi, R.; Motoyoshiya, J.; Nishii, Y. *Chem. Lett.* **2010**, *39*, 194.

23. a) Wheland, G. W. *J. Am. Chem. Soc.* **1942**, *64*, 900; b) Dowdy, D.; Gore, P. H.; Waters, D. N. J. *Chem. Soc., Perkin Trans. 2* **1991**, 1149.

24. For the seminal example of a formal homo-Nazarov cyclizations using alkenyl π-nucleophiles, see: Tsuge, O.; Kanemasa, S.; Otsuka, T.; Suzuki, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2897.

25. We observed that there is no measurable effect on reaction efficiencies (i.e., yield, conversion, reaction time) by switching between methyl or ethyl esters.

26. For the formation of *α*-Diazo compounds **12a-b** see: Phun, L. H.; Patil, D. V.; Cavitt, M. A.; France, S. *Org. Lett.* **2011**, *13*, 1952; for the formation of diazo compounds **12c** and **12g** see: de Nanteuil, F.; Waser, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 12075.

27. For the formation of β-ketoester **11d** see: Sivagurunathan, K.; Kamil, S. R. M.; Syed Shafi, S.; Khan, F. L. A.; Ragavan, R. V. *Tetrahedron Lett.* **2011**, *52*, 1205; for the formation of β-ketoester **11e** see: Li, H.; He, Z.; Guo, X.; Li, W.; Zhao, X.; Li, Z. *Org. Lett.* **2009**, *11*, 4176.

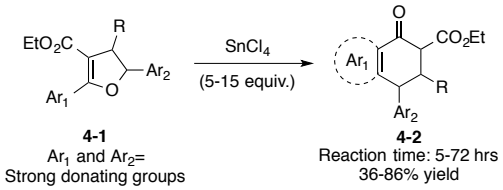
28. For the formation of allenes **13b-d** see: Semba, K.; Shinomiya, M.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Eur. J.* **2013**, *19*, 7125; For the formation of allene **13h** see: Kunugi, A.; Kuwamura, K.; Inoue, M.; Kuwamura, Y.; Abe, K. *Electrochimica Acta* **1996**, *41*, 1987.

CHAPTER 4

CATALYTIC, CASCADE RING-OPENING BENZANNULATIONS OF 2,3-DIHYDROFURAN *O*,*O*- AND *N*,*O*-ACETALS

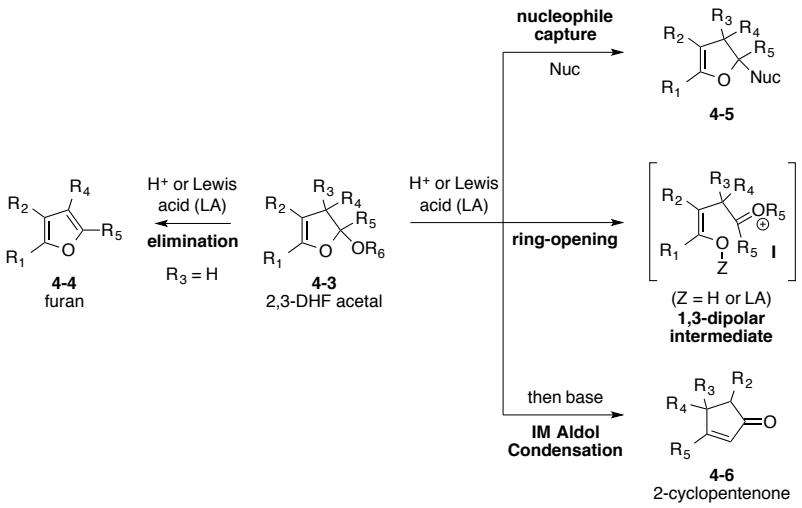
4.1 Introduction

One of the most significant utilities of the 2,3-dihydrofuran (2,3-DHF) subunit relies on their presence in many important biologically active compounds.[1] In addition, they have shown to be extremely useful building blocks in organic synthesis as synthetic precursors for furans (via oxidation[2] or Pd-catalyzed dehydrogenation[3]), tetrahydrofurans and even more complex structures, such as bioactive synthetic molecules,[4] The presence of a donor-acceptor substituted C-C double bond allows them to participate in several cycloadditions and nucleophile/electrophile trapping reactions.[5] Not limited to that, 2,3-DHF have also participated in Pd-catalyzed cross-couplings[6], ring-expansion[7] and cycloisomerizations.[8-9] For instance, the positioning and the nature of the functional groups its very important to tune the reactivity of 2,3-DHF. For example, Fristad and co-workers reported the formation of substituted tetralones **4-2**, a family of bioactive naturally occurring lignans, via ring-opening cycloisomerization of 2,3-dihydrofurans **4-1** (Scheme 4-1). The right positioning of an ester as an acceptor/coordinating group, an aryl as a π-nucleophile (Ar_1), and an aryl donor group (Ar_2) to facilitate the ring-opening was part of the strategy employed on the transformation. However, the conditions required excessive amounts of $SnCl_4$ and long reaction times.[9]



Scheme 4-1. Fristad's reported synthesis of substituted tetralones.

One class of DHFs that has received particular attention from the synthetic community are the 2-alkoxy-2,3-dihydrofurans (or DHF *O*,*O*-acetals). Besides their presence in bioactive natural products containing 5,5- and 5,6-fused bicyclic DHF *O*,*O*-acetals,[4b] the inherent reactivity of the acetal moiety makes DHF acetals useful synthetically. They undergo two primary types of reactivity as described in the literature (Scheme 4-2). First, they serve as precursors for furans **4-4** following acid-promoted alcohol elimination.[10] Second, acid-promoted acetal hydrolysis results in either substitution[11] of the exocyclic alkoxy group (in the presence of a nucleophile) or DHF ring-opening leading to a 1,3-dipolar intermediate (**I**). It is through this dipolar behavior that 2,3-DHF acetals have been employed in cationic ring-opening polymerizations[12] and as a means to access 2-cyclopentenones **4-6** [following base-promoted intramolecular (IM) aldol condensation].[7]

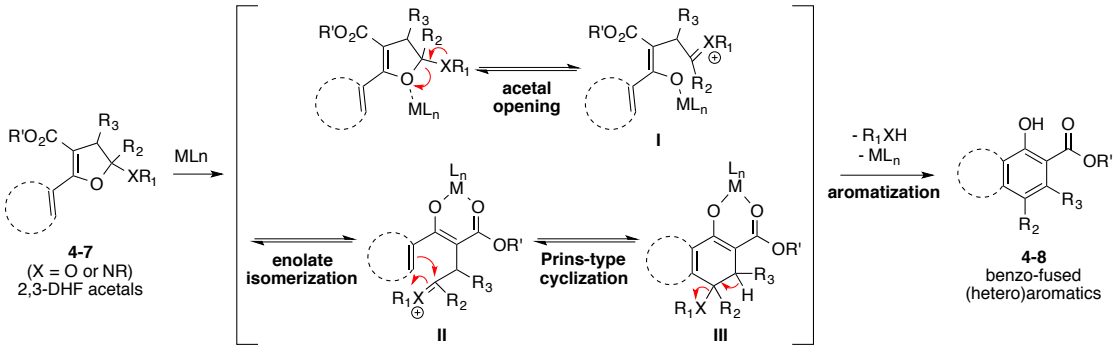


Scheme 4-2. General reactivity of 2,3-DHF acetals.

The development of new chemical transformation to generate (hetero)aromatics has become an important area of research in organic chemistry due to their prevalence in important frameworks with broad application in natural products synthesis, medicinal chemistry, chemical biology, and materials science.[13] Our group and others have examined Lewis acid-catalyzed or -mediated ring-opening cyclizations of activated cyclopropanes, alkylidene cyclopropanes, and cyclopropenes for the formation of these aromatic polycycles.[14] Encouraged by finding new benzannulation transformations, we sought to explore 2,3-DHF acetals as a general approach to functionalized benzo-fused (hetero)aromatics.

Herein, we disclose an $Al(OTf)_3$-catalyzed, cascade ring-opening benzannulation of 5-(hetero)aryl-2,3-dihydrofuran *O*,*O*- and *N*,*O*-acetals **4-7** (Scheme 4-3). The proposed cascade reaction involves initial dihydrofuran acetal ring-opening in the presence of the Lewis acid. Upon ring-opening, the resulting alkoxonium (or iminium) intermediate **I** undergoes enolate isomerization to form a six-membered Lewis acid-enolate chelate complex

II. Next, a Prins-type[15] cyclization occurs to form intermediate **III**, which readily aromatizes via elimination of RXH to form the benzo-fused product **4-8**. **This transformation provides a powerful approach for the synthesis of benzenoid compounds and represents novel reactivity for DHFs.**[16]

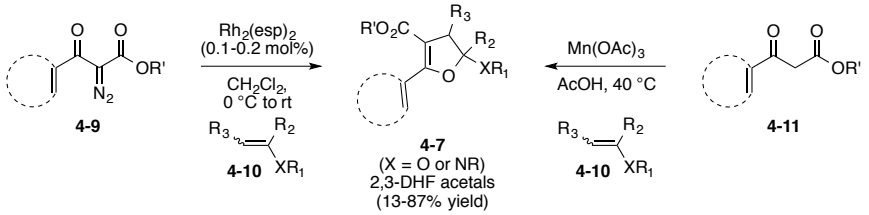


Scheme 4-3. Cascade ring-opening-Prins-Type benzannulations of 2,3-DHF *O*,*O*- and *N*,*O*-acetals.

4.2 Results and Discussion

4.2.1 Synthetic methods

DHF acetals are readily prepared in good yields via Rh(II)-catalyzed reactions[17] of α-diazo-β-ketoesters **4-9** with hetero-olefins **4-10** or Mn(III)-mediated reactions[7] of β-ketoesters **4-11** with hetero-olefins **4-10** (Scheme 4-4).

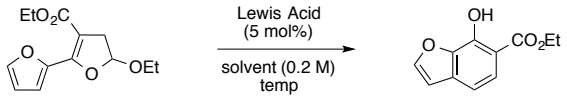


Scheme 4-4. Synthesis of 2,3-DHF *O*,*O*- and *N*,*O*-acetals.

4.2.2 Reaction optimization

In order to optimize the cascade transformation, we chose to employ dihydrofuran acetal **4-7a** as the model system. Given the relative instability of the furan unit in the presence of certain Lewis acids, we anticipated successful optimization of this substrate would bode well for broader exploration of substrate scope (Table 4-1). Starting with $In(OTf)_3$, mainly degradation was observed with only 5% of the desired benzofuran **4-8a** isolated (Table 4-1, entry 1). Degradation or poor conversions were observed with other Lewis acids, such as $Sc(OTf)_3$, $Cu(OTf)_2$, and $Yb(OTf)_3$. More tangible amounts of **4-8a** were obtained with $Ga(OTf)_3$ and $Al(OTf)_3$ (Table 4-1, entries 2 and 3). Performing the reaction at reflux with $Al(OTf)_3$ afforded **4-8a** in 35% yield (Table 4-1, entry 4). Changing the solvent to toluene and performing the reaction at reflux gave 40% yield (Table 4-1, entry 5). Reducing the temperature to 85˚C was found to increase the yield to 46% (Table 4-1, entry 6). All other attempts to further optimize the reaction (e.g., changing temperature, catalyst loading, concentration, etc.) failed to provide improved yields. Therefore, the conditions used for the examination of reaction scope were 5 mol % $Al(OTf)_3$ in toluene at 85 ˚C.

Table 4-1. Optimization of the cascade reaction.



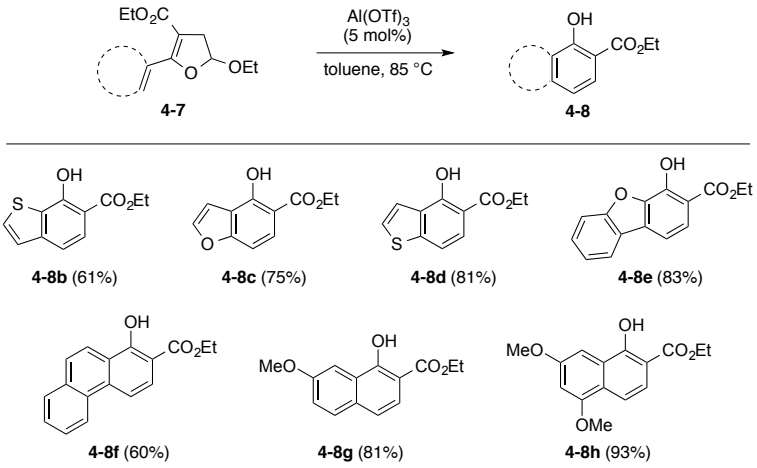
4-7a **4-8a**

Entry[a]	Lewis acid	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	$In(OTf)_3$	CH_2Cl_2	23	45.0	5
2	$Ga(OTf)_3$	CH_2Cl_2	23	9.5	16
3	$Al(OTf)_3$	CH_2Cl_2	23	45.0	19
4	$Al(OTf)_3$	CH_2Cl_2	40	6.5	35
5	$Al(OTf)_3$	toluene	110	1.0	40
6	$Al(OTf)_3$	toluene	85	1.0	46

a) Reaction conditions: Lewis acid (5 mol%), **4-7a**, and solvent (0.2 M) at the indicated temperature;
b) Isolated yield after column chromathography.

4.2.3 Reaction scope

With a working method in hand, the cascade reaction with other (hetero)aryl dihydrofuran derivatives were evaluated (Scheme 4-5). 2-Thienyl dihydrofuran **4-7b** was readily converted to the benzothiophene **4-8b** in 61% yield. 3-Furyl and 3-thienyl derivatives **4-7c** and **4-7c** provided the corresponding benzofuran **4-8c** and benzothiophene **4-8d** in 75% and 81% yield, respectively. As anticipated, benzofuryl dihydrofuran **4-7e** generated the dibenzo[*b*,*d*]furan **4-8e** in 83% yield. The 2-napthyl substrate **4-7f** afforded phenanthrene **4-8f** in 60% yield as the only regioisomer. 3-Methoxyphenyl dihydrofuran **4-7g** similarly gave naphthalene **4-8g** as the only regioisomer in 81% yield. High yield (93%) was observed for the cascade reaction of 3,5-dimethoxy dihydrofuran **4-7h** to give naphthalene **4-8h**.

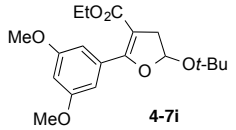
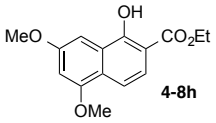
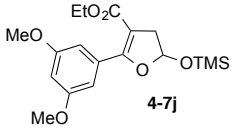
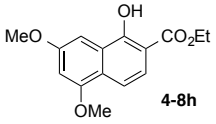
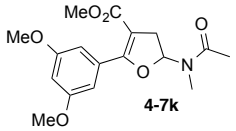
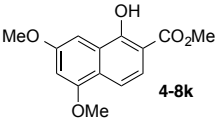
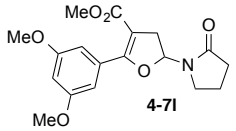
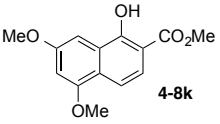


Scheme 4-5. Al(OTf)$_3$-catalyzed cascade ceactions of DHF acetals 4-7.

Next, the effect of changing the nature of the acetal group on reaction efficiency was evaluated (Table 4-2). Dihydrofuran *O*,*O*- and *N*,*O*-acetals **4-7i** to **4-7l** were prepared and subjected to the optimized cascade conditions. When dihydrofuran **4-7i** (containing a *tert*-butoxy group) was used, naphthalene **4-8h** was obtained in 88% yield (Table 4-2, entry 1).

The siloxy derivative **4-7j** afforded smooth conversion to **4-8h** in 80% yield (Table 4-2, entry 2). Methyl acetamido DHF **4-7k** provided **4-8k** with comparable yield (95%) to 2-ethoxy DHF **4-7h** but with a longer reaction (Table 4-2, entry 3). Finally, pyrrolidin-2-one **4-7l** gave a modest 51% yield of **4-8k** (Table 4-2, entry 4).

Table 4-2. Probing the effect by changing the acetal group.

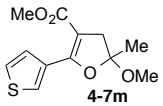
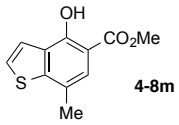
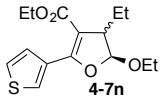
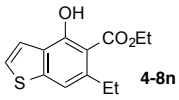
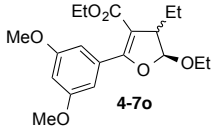
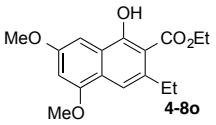
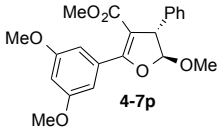
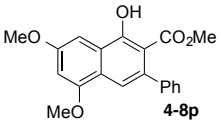
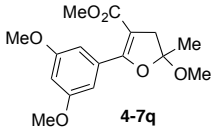
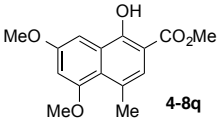
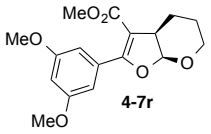
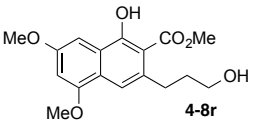
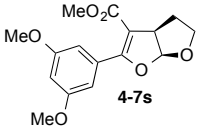
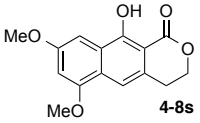
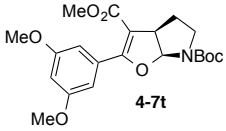
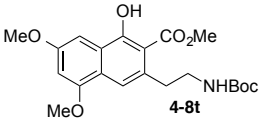
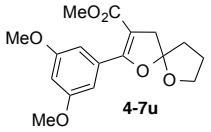
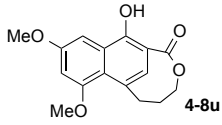
Entry[a]	DHF (4-7)	Product (4-8)	Time (h)	Yield (%)[b]
1	 **4-7i**	 **4-8h**	0.67	88
2	 **4-7j**	 **4-8h**	0.67	80
3	 **4-7k**	 **4-8k**	5.0	95
4	 **4-7l**	 **4-8k**	21	51

a) Reaction conditions: $Al(OTf)_3$ (5 mol%), **4-7**, and toluene (0.2 M) at 85 °C; b) Isolated yield after column chromathography.

To fully broaden the reaction scope, more substituted DHF acetals (tetra-substituted DHF derivatives) were synthesized and explored. When 2-methoxy-2-methyl 5-thienyl DHF **4-7m** was subjected to the optimized conditions, none of the expected 7-methyl benzothiophene **4-8m** was observed and furan **4-4m** was formed instead. Interestingly, when the temperature was reduced to 70 ˚C and a drop of water was added to the reaction mixture, a 1:1.18 crude mixture of **4-8m** to furan **4-4m** was observed. After some optimization, it was found that 20 mol% $Al(OTf)_3$ in toluene with a drop of water at 70 ˚C provided **4-8m** in 80%

yield (Table 4-3, entry 1). It is plausible that the water may be promoting the formation of a dihydrofuran hemiacetal intermediate that may facilitate ring-opening over furan formation. Under these new conditions, the 3-ethyl-2-methoxy 5-thienyl DHF **4-7n** gave the expected 6-ethyl benzothiophene **4-8n** in 69% yield (Table 4-3, entry 2). Similarly with **4-7o** and **4-7p**, the 3-ethyl and 3-phenyl naphthalenes **4-8o** and **4-8m** were formed in 88% and 79% yield, respectively (Table 4-3, entries 3 and 4). In comparison, the 2,2-*gem*-disubstituted acetal **4-7q** afforded the 4-methyl naphthalene **4-8q** in 86% yield (Table 4-3, entry 5). These examples demonstrate the general strength of the method for the strategic synthesis of regioisomeric benzo-fused systems. Since the acetal serves as the directing group for ring opening, the placement of the substituent determines the regiochemistry. Therefore, the selection of the alkene for DHF synthesis becomes an important reaction design component as it will dictate the cascade product regiochemistry. This level of regiocontrol is unprecedented for Lewis acid-promoted benzannulations.

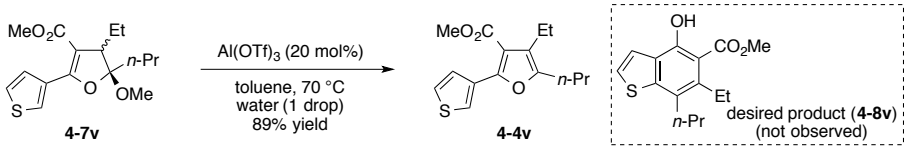
Table 4-3. Cascade reactions of tetra-substituted 2,3-DHF acetals.

Entry[a]	DHF (4-7)	Product (4-8)	Time (h)	Yield (%)[b]
1	 **4-7m**	 **4-8m**	2.0	86
2	 **4-7n**	 **4-8n**	4.0	69
3	 **4-7o**	 **4-8o**	0.67	86
4	 **4-7p**	 **4-8p**	7.0	79
5	 **4-7q**	 **4-8q**	7.5	86
6[c]	 **4-7r**	 **4-8r**	1.0	85
7[c]	 **4-7s**	 **4-8s**	5.0	90
8[c]	 **4-7t**	 **4-8t**	19	17
9	 **4-7u**	 **4-8u**	4.0	47

a) Reaction conditions: $Al(OTf)_3$ (20 mol%), **4-7**, and toluene (0.2 M), water (1 drop), 70 °C; b) Isolated yield after column chromathography; c) Performed using $Al(OTf)_3$ (5 mol%) at 85 °C (no water added); d) Performed using $Al(OTf)_3$ (30 mol%) at 110 °C.

For the fused bicyclic DHF acetals (**4-7r** to **4-7t**), the original reaction conditions [5 mol% $Al(OTf)_3$, 85 ˚C] offered better yields of the expected products. 3a,5,6,7a-Tetrahydro-4*H*-furo[2,3-*b*]pyran **4-7r** gave 85% yield of naphthalene **4-8r**, which contains a pendant

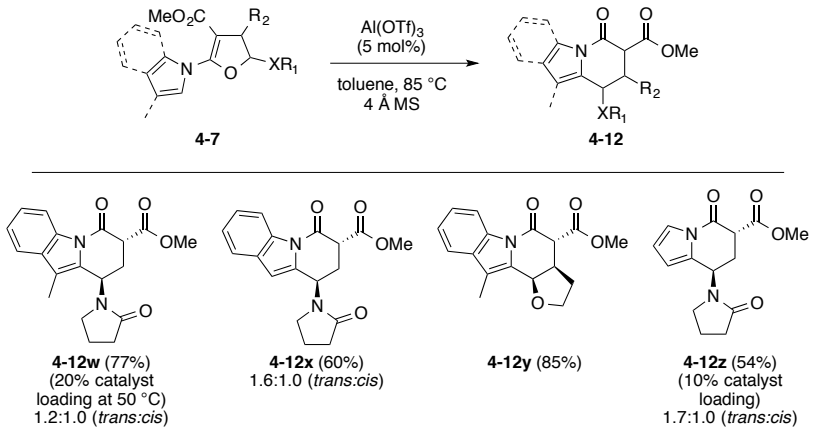
hydroxypropyl unit (Table 4-3, entry 6). In contrast, lactonization was observed for 2,3,3a,6a-tetrahydrofuro[2,3-*b*]furan **4-7s** as the tricyclic 3,4-dihydro-1*H*-benzo[*g*]isochromen-1-one **4-8s** was generated in 90% yield (Table 4-3, entry 7). Finally, 6-Boc-3a,5,6,6a-tetrahydro-4*H*-furo[2,3-*b*]pyrrole **4-7t** (a bicyclic *N*,*O*-acetal) provided 17% yield (52%, BSRM) of naphthalene **4-8t** (Table 4-3, entry 8). The low yield can be attributed to catalyst deactivation by coordination with the pendant carbamate group; thus, requiring increased catalyst loading. Surprisingly, spirocyclic acetal **4-7u** afforded 6,7-dihydro-3*H*,5*H*-2,8-(metheno)benzo[*e*]oxecin-3-one **4-8u** in 47% yield (Table 4-3, entry 9). While formation of the naphthyl ring was expected, macrolactonization to form a bridging eight-membered bicycle was not. This framework is completely unprecedented in the literature. Finally, all attempts to access the expected naphthalene from penta-substituted DHF acetal **4-7v** failed and only furan formation was observed (Scheme 4-6).



Scheme 4-6. Formation of furan 4-4v from penta-substituted DHF 4-7v.

Based on our ongoing interest in the synthesis of indole-containing compounds, a series of DHF acetals substituted at the 5-position with the nitrogen of an indole was prepared and subjected to the initial reaction conditions (Scheme 4-7). In each case, only cycloisomerization was observed and the final elimination/aromatization does not take place. For example, *N*-indole substituted DHF *N*,*O*-acetals **4-7w** and **4-7x** gave the resulting hydropyrido[1,2-*a*]indoles **4-12w** and **4-12x** in 77% and 60% yield, respectively. Similarly,

2-(1*H*-Indol-1-yl)-3a,4,5,6a-tetrahydrofuro[2,3-*b*]furan **4-7y** provided the tetracyclic 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one **4-12y** in 85% yield. Lastly, the corresponding 2-(1*H*-pyrrol-1-yl) DHF *N*,*O*-acetal **4-7z** afforded 7,8-dihydroindolizin-5(6*H*)-one **4-12z** in 54% yield. The barrier to heteroaromatization is presumably too high for compounds **4-12w** to **4-12z** when compared to formation of a benzene ring.



Scheme 4-7. Reactions of 2-(1*H*-indol-1-yl) and 2-(1*H*-pyrrol-1-yl) DHF acetals 4-7w to 4-7z.

4.3 Conclusions

In conclusion, we have developed a powerful new strategy towards accessing functionalized benzo-fused (hetero)aromatics from DHF acetals. The positioning of each functional group was strategic and essential for the benzannulation cascade due to: 1) the anchimeric assistance of the acetal heteroatom allows DHF ring-opening under catalytic conditions; 2) the 1,3-ketoester group provides the bidentate six-membered Lewis acid-enolate chelate; 3) the carbocation is intramolecularly trapped by a π-nucleophile; and 4) the acetal moiety plays an important role in the regiochemistry and its elimination provides the final benzo-fused compound.

Benzofused products are obtained in up to 95% yield using catalytic amounts of $Al(OTf)_3$. The approach offers excellent regiocontrol based on choice of alkene used to form the requisite DHF acetal. Moreover, in the cases of *N*-indolyl or *N*-pyrrolyl substituted DHF acetals, cycloisomerization products are obtained in good yields. This method represents novel reactivity for DHF acetals and allows for future methodologies (inter- and intramolecular) to be developed with DHF acetals as a versatile synthetic building block. Future work will involve: (1) utilization of the method to access several naturally-occurring compounds; (2) improving the product yields of the fused bicyclic *N*,*O*-acetals; and (3) accessing benzannulated products from pentasubstituted DHF acetals.

4.4 Experimental

4.4.1. General Methods

All reactions were carried out in pre-dried glassware from the oven and any additional moisture was removed by flame-drying the reaction vessel under vacuum. Each reaction proceeded under a nitrogen atmosphere with anhydrous solvents. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenoneketyl under nitrogen and stored in a Schlenk flask. 1,2-Dichloroethane and dichloromethane were purified by distillation from calcium hydride. Anhydrous toluene and acetonitrile was purchased from EMD Chemicals and used without further purification. Methyl- and ethyl acetate were fractionally distilled over P_2O_5. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification. β-ketoester compounds **4-11a** and **4-11b** were synthesized as previously reported.[18] α-Diazo compounds **4-9k**, **4-9m**, **4-9w**, **4-9x**, and **4-9z** were synthesized as

previously reported.[14] Enol ethers **4-10p**, **4-10u** and **4-10v** were synthesized as previously reported. 2,3-DHF **4-7y** was synthesized as previously reported.[14b]

Chromatographic purification was performed as flash chromatography with Dynamic Adsorbents silica gel (32-65 μm) and solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F_{254} TLC glass plates. Visualization was accomplished with UV light or iodine chamber. Each yield refers to an isolated, analytically-pure material.

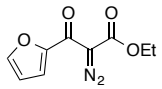
Infrared (IR) spectra were obtained using a Bruker alpha FTIR with an ATR attachment. The IR bands are characterized as weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on Variant 300 MHz, Bruker Avance 400 MHz or 500 MHz spectrometer with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a VG-70SE instrument. Uncorrected melting points were measured with a digital melting point apparatus (DigiMelt MPA 160).

4.4.2. Experimental Procedures

a. Formation of α-diazo compounds 4-9a to 4-9h

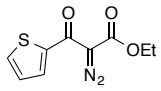
General Diazo Transfer Procedure: To a solution of β-ketoester **4-11** (1 equiv.) in CH_3CN (0.5-1.0 M) was added triethylamine (1.2 equiv.) at RT. After 5 min of vigorous stirring,

tosyl azide (1.2 equiv.) was added and the reaction was stirred for 3 h at room temperature. At this point, the reaction mixture was concentrated *in vacuo* and purified via silica gel flash chromatography (eluting with EtOAc:Hexanes or Et_2O:Hexanes) to isolate the product.



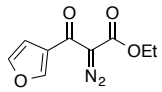
4-9a

Ethyl 2-diazo-3-(furan-2-yl)-3-oxopropanoate (4-9a). The general procedure was followed using β-ketoester **4-11a** (27.2 g, 149 mmol) in CH_3CN (150.0 mL), triethylamine (25.0 mL, 180 mmol) and tosyl azide (35.3 g, 179 mmol). The reaction mixture was concentrated under reduced pressure and purified via column chromatography (15% EtOAc/hexane, R_f = 0.20) to afford diazo **4-9a** (25.8 g, 83%) as a bright yellow oil. Spectral data matches with reported values.[19]



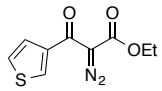
4-9b

Ethyl 2-diazo-3-oxo-3-(thiophen-2-yl)propanoate (4-9b). The general procedure was followed using β-ketoester **4-11b** (4.21 g, 21.2 mmol) in CH_3CN (43.0 mL), triethylamine (3.6 mL, 26.0 mmol) and tosyl azide (5.03 g, 25.5 mmol). The reaction mixture was concentrated under reduced pressure and purified via column chromatography (15% EtOAc/hexane, R_f = 0.16) to afford diazo **4-9b** (4.75 g, 99%) as a bright yellow oil. Spectral data matches with reported values.[19]



4-9c

Ethyl 2-diazo-3-(furan-3-yl)-3-oxopropanoate (4-9c). The general procedure was followed using commercially available β-ketoester **4-11c** (2.85 g, 15.6 mmol) in CH_3CN (32.0 mL), triethylamine (2.6 mL, 18.6 mmol) and tosyl azide (3.70 g, 18.8 mmol). The reaction mixture was concentrated under reduced pressure and purified via column chromatography (15% EtOAc/hexane, R_f = 0.23) to afford diazo **4-9c** (3.22 g, 99%) as a bright yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.41 - 8.45 (m, 1 H), 7.39 - 7.42 (m, 1 H), 6.86 - 6.89 (m, 1 H), 4.28 (q, J = 7.5 Hz, 2 H), 1.34 (t, J = 7.5 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 177.7, 160.8, 148.9, 142.6, 124.8, 110.2, 78.0, 61.4, 14.2. **IR**: 2983.9 (w), 2133.3 (s), 1716.7 (s), 1373.3 (m), 1166.9 (m). **HRMS** (ESI) *m/z*: [M-Na^+] calcd. for $C_9H_8O_4N_2Na$, 231.0376; found, 231.0372.



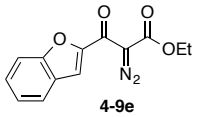
4-9d

Ethyl 2-diazo-3-oxo-3-(thiophen-3-yl)propanoate (4-9d).

*Preparation of Ethyl 3-oxo-3-(thiophen-3-yl)propanoate (**4-11d**).* To a solution of LHMDS (1.0 M in THF, 40.5 mL, 40.5 mmol) at -78 °C was added EtOAc (2.0 mL, 20.3 mmol) in one shot. The reaction mixture was stirred at -78 °C for 45 min prior the addition of thiophene-3-carbonyl chloride (2.83 g, 19.3 mmol) in THF (30.0 mL). After stirring for 30 min at -78 °C, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc (3x), dried over Na_2SO_4, and purified via column chromatography (15% Et_2O/hexane, R_f = 0.22)

to afford β-ketoester **4-11d** (3.08 g, 81%) as a bright yellow oil. Spectral data matches with reported values.[20]

*Preparation of **4-9d**.* The general procedure was followed using β-ketoester **4-11d** (3.07 g, 15.5 mmol) in CH_3CN (31.0 mL), triethylamine (2.6 mL, 18.6 mmol) and tosyl azide (3.68 g, 18.7 mmol). The reaction mixture was concentrated under reduced pressure and purified via column chromatography to afford diazo **4-9d** (3.37 g, 97%) as a bright yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.14 - 8.20 (m, 1 H), 7.44 - 7.51 (m, 1 H), 7.23 - 7.29 (m, 1 H), 4.23 - 4.33 (m, 2 H), 1.26 - 1.34 (m, 3 H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 179.2, 160.9, 139.0, 132.7, 127.9, 124.8, 61.5, 14.2; diazo C not observed. **IR**: 3109.3 (w), 2983.8 (w), 2135.2 (s), 1714.7 (s), 1587.4 (m), 1311.59 (s), 1107.14 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_9H_8O_3N_2S$, 224.0256; found, 224.0259.



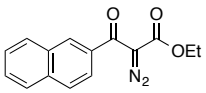
4-9e

Ethyl 3-(benzofuran-2-yl)-2-diazo-3-oxopropanoate (4-9e).

*Preparation of Ethyl 3-(benzofuran-2-yl)-3-oxopropanoate (**4-11e**).* To a solution of LHMDS (1.0 M in THF, 32.4 mL, 32.4 mmol) at -78 °C was added EtOAc (1.6 mL, 16.3 mmol) in one shot. The reaction mixture was stirred at -78 °C for 45 min prior the addition of benzofuran-2-carbonyl chloride (2.78 g, 15.4 mmol) in THF (30.0 mL). After stirring for 30 min at -78 °C, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc (3x), dried over Na_2SO_4, and purified via column chromatography (15% Et_2O/hexane, R_f = 0.35)

to afford β-ketoester **4-11e** (2.68 g, 67%) as a orange oil. Spectral data matches with reported values.[21]

*Preparation of **4-9e**.* The general procedure was followed using β-ketoester **4-11e** (2.66 g, 11.5 mmol) in CH_3CN (23.0 mL), triethylamine (1.9 mL, 13.7 mmol) and tosyl azide (2.71 g, 13.7 mmol). The reaction mixture was concentrated under reduced pressure and purified via column chromatography (15% Et_2O/hexane, R_f = 0.16) to afford diazo **4-9e** (1.89 g, 64%) as a bright yellow solid (mp: 75-77 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.82 (s, 1 H), 7.68 (d, *J* = 7.9 Hz, 1 H), 7.53 (d, *J* = 8.2 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 1 H), 7.22 - 7.33 (m, 1 H), 4.34 (q, *J* = 7.0 Hz, 2 H), 1.33 (t, *J* = 7.0 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.2, 160.6, 154.9, 150.4, 128.0, 126.7, 123.7, 123.2, 114.9, 112.0, 75.4, 61.7, 14.1. **IR**: 2982.0 (w), 2142.9 (s), 1730.2 (s), 1612.5 (m), 1305.8 (s), 1103.3 (m). **HRMS** (EI) *m/z*: [M-Na$^+$] calcd. for $C_{13}H_{10}O_4N_2Na$, 281.0533; found, 281.0525.



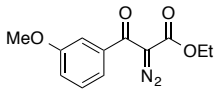
4-9f

Ethyl 2-diazo-3-(naphthalen-2-yl)-3-oxopropanoate (4-9f).

*Preparation of Ethyl 3-(naphthalen-2-yl)-3-oxopropanoate (**4-11f**).* To a solution of LHMDS (1.0 M in THF, 33.0 mL, 33.0 mmol) at -78 °C was added EtOAc (1.6 mL, 16.3 mmol) in one shot. The reaction mixture was stirred at -78 °C for 45 min prior the addition of 2-naphthoyl chloride (3.02 g, 15.8 mmol) in THF (30.0 mL). After stirring for 30 min at -78 °C, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc (3x), dried over

Na_2SO_4, and purified via column chromatography (10% Et_2O/hexane, R_f = 0.16) to afford β-ketoester **4-11f** (3.30 g, 86%) as a orange oil. Spectral data matches with reported values.[22]

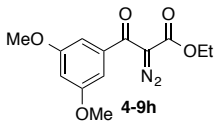
*Preparation of **4-9f**.* The general procedure was followed using β-ketoester **4-11f** (3.27 g, 13.5 mmol) in CH_3CN (27.0 mL), triethylamine (2.3 mL, 16.6 mmol) and tosyl azide (3.19 g, 16.2 mmol). The reaction mixture was concentrated under reduced pressure and purified via column chromatography (10% Et_2O/hexane, R_f = 0.14) to afford diazo **4-9f** (3.45 g, 95%) as a bright yellow solid (mp: 60-61 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.18 (s, 1 H), 7.92 (d, *J* = 8.2 Hz, 1 H), 7.87 (d, *J* = 8.2 Hz, 2 H), 7.70 (dd, *J* = 8.5, 1.8 Hz, 1 H), 7.55 - 7.62 (m, 1 H), 7.49 - 7.55 (m, 1 H), 4.26 (q, *J* = 7.2 Hz, 2 H), 1.24 (t, *J* = 7.2 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.7, 161.1, 135.1, 134.3, 132.1, 129.6, 129.2, 128.1, 127.8, 127.5, 126.6, 124.6, 76.4, 61.6, 14.2. **IR**: 3061.0 (w), 2982.0 (w), 2144.6 (s), 1718.6 (s), 1618.3 (m), 1303.88 (s), 1107.1 (m). **HRMS** (EI) *m/z*: [M-Na^+] calcd. for $C_{15}H_{12}O_3N_2Na$, 291.0740; found, 291.0738.



4-9g

Ethyl 2-diazo-3-(3-methoxyphenyl)-3-oxopropanoate (4-9g). The general procedure was followed using commercially available β-ketoester **4-11g** (3.01 g, 13.5 mmol) in CH_3CN (25.0 mL), triethylamine (2.3 mL, 16.6 mmol) and tosyl azide (3.20 g, 16.2 mmol). The reaction mixture was concentrated under reduced pressure and purified via column chromatography (15% Et_2O/hexane, R_f = 0.15) to afford diazo **4-9g** (2.16 g, 64%) as a bright yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.29 - 7.34 (m, 1 H), 7.17 - 7.22 (m, 1 H), 7.15

(dd, J = 2.4, 1.5 Hz, 1 H), 7.06 (ddd, J = 8.2, 2.4, 0.9 Hz, 1 H), 4.24 (q, J = 7.0 Hz, 2 H), 3.82 (s, 3 H), 1.25 (t, J = 7.0 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.5, 160.9, 159.1, 138.2, 128.8, 120.7, 118.3, 113.1, 76.0, 61.6, 55.3, 14.1. **IR**: 2982.0 (w), 2133.3 (s), 1718.6 (s), 1302.0 (s), 1111.0 (s). **HRMS** (ESI) *m/z*: [M-Na^+] calcd. for $C_{12}H_{12}O_4N_2Na$, 271.0689; found, 271.0679.



4-9h

Ethyl 2-diazo-3-(3,5-dimethoxyphenyl)-3-oxopropanoate (4-9h).

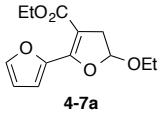
*Ethyl 3-(3,5-dimethoxyphenyl)-3-oxopropanoate (**4-11h**).* To a solution of LHMDS (1.0 M in THF, 31.5 mL, 31.5 mmol) at -78 °C was added EtOAc (1.5 mL, 15.3 mmol) in one shot. The reaction mixture was stirred at -78 °C for 45 min prior the addition of 3,5-dimethoxybenzoyl chloride (2.90 g, 14.5 mmol) in THF (30.0 mL). After stirring for 30 min at -78 °C, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc (3x), dried over Na_2SO_4, and purified via column chromatography (10% Et_2O/hexane, R_f = 0.07) to afford β-ketoester **4-11h** (2.49 g, 68%) as a colorless oil. Spectral data matches with reported values.[23]

*Preparation of **4-9h**.* The general procedure was followed using β-ketoester **4-11h** (2.46 g, 9.75 mmol) in CH_3CN (20.0 mL), triethylamine (1.7 mL, 12.3 mmol) and tosyl azide (2.30 g, 11.7 mmol). The reaction mixture was concentrated under reduced pressure and purified via column chromatography (15% Et_2O/hexane, R_f = 0.10) to afford diazo **4-9h** (2.51 g, 93%) as

a bright yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.75 (d, *J* = 2.4 Hz, 2 H), 6.60 (t, *J* = 2.4 Hz, 1 H), 4.25 (q, *J* = 7.2 Hz, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.4, 160.9, 160.3, 138.8, 106.1, 104.4, 76.0, 61.6, 55.5, 14.2. **IR**: 3007.0 (w), 2941.4 (w), 2839.2 (w), 2129.4 (s), 1722.4 (s), 1591.3 (s), 1305.8 (s), 1155.4 (s). **HRMS** (EI) *m/z*: [M-Na^+] calcd. for $C_{13}H_{14}O_5N_2Na$, 301.0795; found, 301.0790.

b. Formation of 2,3-dihydrofuran acetals 7-9a to 7-9z

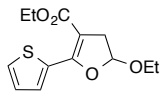
General DHF Formation Procedure: A pre-dried round bottom flask was charged with Rh_2esp_2 (0.1-0.2 mol%) and CH_2Cl_2 (2.0-4.0 mL). After cooling the solution to 0 °C, the corresponding alkene (1.0-3.0 equiv.) was added to the reaction vessel. A precooled solution of the α-diazo ester (1.0-1.3 equiv.) in CH_2Cl_2 (0.25-0.50 M) was then added to the reaction in one shot, keeping the reaction mixture at 0 °C. After stirring for 2 h at 0 °C, the ice bath was removed and the reaction was allowed to warm up to rt and stirred for 1-2 hr. After complete consumption of the diazo compound, the reaction was quenched with saturated aqueous thiourea and allowed to stir for 30 minutes. The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (2x). The organic layer was washed with brine, dried with Na_2SO_4, concentrated, and column chromatography afforded the desired 2,3-dihydrofuran acetal.



4-7a

Ethyl 5-ethoxy-4,5-dihydro-[2,2'-bifuran]-3-carboxylate (4-7a). The general protocol was followed using a solution of Rh_2esp_2 (16.6 mg, 21.9 μmol) in CH_2Cl_2 (20 mL), ethyl vinyl

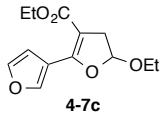
ether (1.56 g, 21.6 mmol), and diazo **4-9a** (5.00 g, 24.0 mmol) in CH_2Cl_2 (24 mL). The reaction was quenched and column chromatography (10% Et_2O/hexane, R_f = 0.23) afforded **4-7a** (2.50 g, 49%) as a light yellow solid (mp: 61-63 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 3.7 Hz, 1H), 7.52 (d *J* = 1.8 Hz, 1H), 6.52 (dd, *J* = 3.7, 1.8 Hz, 1H), 5.67 (dd, *J* = 7.3, 2.7 Hz, 1H), 4.20 (m, 2H), 3.96 (dq, *J* = 9.5, 7.1 Hz, 1H), 3.65 (dq, *J* = 9.5, 7.1 Hz, 1H), 3.23 (dd, *J*=16.9, 7.3 Hz, 1H), 2.94 (dd, *J*=16.9, 2.7 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 164.3, 152.6, 144.4, 143.9, 117.6, 111.9, 104.6, 100.8, 64.3, 59.8, 37.9, 15.0, 14.4. **IR**: 2980.3 (w), 1733.9 (s), 1674.8 (s), 1464.6 (m), 1013.4 (s), 767.0 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{13}H_{16}O_5$, 252.0998; found, 252.0997.



4-7b

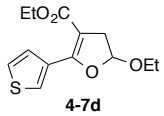
Ethyl 5-ethoxy-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate (4-7b). The general protocol was followed using a solution of Rh_2esp_2 (1.8 mg, 2.3 μmol) in CH_2Cl_2 (2.0 mL), ethyl vinyl ether (126 mg, 1.75 mmol), and diazo **4-9b** (497 mg, 2.22 mmol) in CH_2Cl_2 (4.5 mL). The reaction was quenched and column chromatography (10% Et_2O/hexane, R_f = 0.24) afforded **4-7b** (338 mg, 72%) as a white solid (mp: 35-36 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.21 (dd, *J* = 3.9, 1.1 Hz, 1H), 7.49 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.10 (dd, *J* = 5.0, 3.9 Hz, 1H), 5.63 (dd, *J* = 7.3, 2.5 Hz, 1H), 4.15 - 4.30 (m, 2H), 3.94 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.66 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.25 (dd, *J* = 16.8, 7.3 Hz, 1H), 2.97 (dd, *J* = 16.8, 2.5 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.9, 156.5, 132.1, 131.6, 130.0, 127.1, 104.0, 100.3, 64.2, 59.9, 38.4, 15.2, 14.4. **IR**: 3102.7 (w), 2979.4 (w),

1732.7 (s), 1659.0 (s), 1516.7 (m), 1411.6 (s), 1242.0 (s), 1056.6 (m), 730.4 (s). **HRMS** (ESI) *m/z*: [M-Na$^+$] calcd. for $C_{13}H_{16}O_4NaS$, 291.0662; found, 291.0659.



4-7c

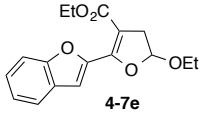
Ethyl 5-ethoxy-4,5-dihydro-[2,3'-bifuran]-3-carboxylate (4-7c). The general protocol was followed using a solution of Rh_2esp_2 (1.4 mg, 1.8 μmol) in CH_2Cl_2 (2.0 mL), ethyl vinyl ether (134 mg, 1.86 mmol), and diazo **4-9c** (509 mg, 2.45 mmol) in CH_2Cl_2 (5.0 mL). The reaction was quenched and column chromatography (10% Et_2O/hexane, R_f = 0.28) afforded **4-7c** (234 mg, 50%) as a light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.43 - 8.48 (m, 1H), 7.38 - 7.44 (m, 1H), 6.97 - 7.03 (m, 1H), 5.57 - 5.64 (m, 1H), 4.13 - 4.27 (m, 2H), 3.86 - 3.96 (m, 1H), 3.58 - 3.69 (m, 1H), 3.19 (dd, *J* = 16.6, 7.3 Hz, 1H), 2.91 (dd, *J* = 16.6, 2.8 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.0, 156.4, 146.8, 142.4, 116.5, 110.1, 104.1, 101.0, 64.1, 59.7, 37.9, 15.1, 14.4. **IR**: 2979.7 (w), 2938.6 (w), 1734.9 (s), 1678.4 (s), 1156.2 (s). **HRMS** (ESI) *m/z*: [M-H$^+$] calcd. for $C_{13}H_{17}O_5$, 253.1071; found, 253.1069.



4-7d

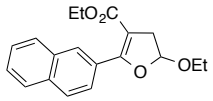
Ethyl 5-ethoxy-2-(thiophen-3-yl)-4,5-dihydrofuran-3-carboxylate (4-7d). The general protocol was followed using a solution of Rh_2esp_2 (3.7 mg, 4.8 μmol) in CH_2Cl_2 (4.0 mL), ethyl vinyl ether (295 mg, 4.09 mmol), and diazo **4-9d** (1.00 g, 4.46 mmol) in CH_2Cl_2 (9.0 mL). The reaction was quenched and column chromatography (10% Et_2O/hexane, R_f = 0.29)

afforded **4-7d** (403 mg, 37%) as a light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.43 (dd, *J* = 3.1, 1.2 Hz, 1H), 7.76 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.28 (dd, *J* = 5.2, 3.1 Hz, 1H), 5.61 (dd, *J* = 7.3, 2.4 Hz, 1H), 4.13 - 4.26 (m, 2H), 3.93 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.65 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.24 (dd, *J* = 16.6, 7.3 Hz, 1H), 2.95 (dd, *J* = 16.6, 2.4 Hz, 1H), 1.23 - 1.31 (m, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.0, 157.8, 130.9, 130.2, 128.4, 124.4, 103.8, 100.9, 64.1, 59.8, 38.3, 15.2, 14.4. **IR**: 3112.4 (w), 2978.9 (w), 1734.2 (s), 1675.8 (s), 1508.1 (m), 1248.9 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{13}H_{16}O_4S$, 268.0769; found, 268.0760.



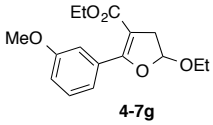
4-7e

Ethyl 2-(benzofuran-2-yl)-5-ethoxy-4,5-dihydrofuran-3-carboxylate (4-7e). The general protocol was followed using a solution of Rh_2esp_2 (1.3 mg, 1.7 μmol) in CH_2Cl_2 (2.0 mL), ethyl vinyl ether (92.3 mg, 1.28 mmol), and diazo **4-9e** (355 mg, 1.37 mmol) in CH_2Cl_2 (4.1 mL). The reaction was quenched and column chromatography (7% Et_2O/hexane, R_f = 0.16) afforded **4-7e** (172 mg, 45%) as a light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.55 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.37 (td, *J* = 7.8, 1.2 Hz, 1H), 7.23 - 7.28 (m, 1H), 5.74 (dd, *J* = 7.2, 2.6 Hz, 1H), 4.18 - 4.32 (m, 2H), 4.02 (dq, *J* = 9.6, 7.2 Hz, 1H), 3.70 (dq, *J* = 9.6, 7.2 Hz, 1H), 3.29 (dd, *J* = 17.1, 7.2 Hz, 1H), 3.01 (dd, *J* = 17.1, 2.6 Hz, 1H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.24 - 1.29 (t, *J* = 7.2, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 164.2, 154.6, 152.7, 145.5, 128.0, 126.3, 123.2, 122.2, 113.6, 111.6, 104.7, 103.9, 64.4, 60.0, 38.2, 15.0, 14.4. **IR**: 2979.9 (w), 2929.3 (w), 1736.1 (s), 1682.4 (s), 1555.5 (s), 1258.2 (s), 1139.9 (s), 753.1 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{17}H_{18}O_5$, 302.1154; found, 302.1164.



4-7f

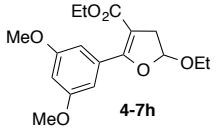
Ethyl 5-ethoxy-2-(naphthalen-2-yl)-4,5-dihydrofuran-3-carboxylate (4-7f). The general protocol was followed using a solution of Rh_2esp_2 (1.3 mg, 1.7 μmol) in CH_2Cl_2 (2.0 mL), ethyl vinyl ether (125 mg, 1.73 mmol), and diazo **4-9f** (503 mg, 1.87 mmol) in CH_2Cl_2 (5.9 mL). The reaction was quenched and column chromatography (10% Et_2O/hexane, R_f = 0.23) afforded **4-7f** (280 mg, 52%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.37 (s, 1 H), 7.87 - 7.93 (m, 2 H), 7.81 - 7.86 (m, 2 H), 7.46 - 7.58 (m, 2 H), 5.70 (dd, *J* = 7.6, 2.7 Hz, 1 H), 4.09 - 4.23 (m, 2 H), 4.00 (dq, *J* = 9.6, 7.2 Hz, 1 H), 3.70 (dq, *J* = 9.6, 7.0 Hz, 1 H), 3.33 (dd, *J* = 16.5, 7.6 Hz, 1 H), 3.03 (dd, *J* = 16.5, 2.7 Hz, 1 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 1.21 (t, *J* = 7.2 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 164.9, 162.8, 134.1, 132.4, 129.8, 128.8, 127.6, 127.4, 127.1, 127.0, 126.2, 126.2, 104.2, 102.5, 64.3, 59.8, 38.5, 15.2, 14.3. **IR**: 3071.0 (w), 2981.4 (w), 1734.9 (s), 1683.8 (s), 1124.7 (m). **HRMS** (ESI) *m/z*: [M-H$^+$] calcd. for $C_{19}H_{21}O_4$, 313.1434; found, 313.1431.



4-7g

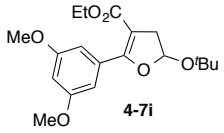
Ethyl 5-ethoxy-2-(3-methoxyphenyl)-4,5-dihydrofuran-3-carboxylate (4-7g). The general protocol was followed using a solution of Rh_2esp_2 (1.2 mg, 1.6 μmol) in CH_2Cl_2 (2.0 mL), ethyl ninyl ether (94.1 mg, 1.30 mmol), and diazo **4-9g** (367 mg, 1.48 mmol) in CH_2Cl_2 (4.4 mL). The reaction was quenched and column chromatography (10% Et_2O/hexane, R_f = 0.18) afforded **4-7g** (269 mg, 71%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.39 - 7.44

(m, 2 H), 7.27 - 7.33 (m, 1 H), 6.94 - 6.99 (m, 1 H), 5.63 (dd, J = 7.3, 2.7 Hz, 1 H), 4.08 - 4.19 (m, 2 H), 3.94 (dq, J = 9.5, 7.0 Hz, 1 H), 3.83 (s, 3 H), 3.65 (dq, J = 9.5, 7.0 Hz, 1 H), 3.26 (dd, J = 16.5, 7.3 Hz, 1 H), 2.96 (dd, J = 16.5, 2.7 Hz, 1 H), 1.26 (t, J = 7.0 Hz, 3 H), 1.21 (t, J = 7.0 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 164.7, 162.5, 158.8, 131.2, 128.6, 121.8, 116.2, 114.7, 104.1, 102.3, 64.2, 59.7, 55.3, 38.4, 15.1, 14.2. **IR**: 2979.6 (w), 2835.7 (w), 1730.6 (s), 1686.3 (s), 1583.2 (m), 1261.4 (s), 1032.0 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{16}H_{20}O_5$, 292.1311; found, 292.1301.



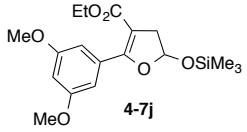
4-7h

Ethyl 2-(3,5-dimethoxyphenyl)-5-ethoxy-4,5-dihydrofuran-3-carboxylate (4-7h). The general protocol was followed using a solution of Rh_2esp_2 (1.3 mg, 1.7 μmol) in CH_2Cl_2 (2.0 mL), ethyl vinyl ether (87.0 mg, 1.21 mmol), and diazo **4-9h** (359 mg, 1.29 mmol) in CH_2Cl_2 (3.5 mL). The reaction was quenched and column chromatography (15% Et_2O/hexane, R_f = 0.15) afforded **4-7h** (212 mg, 55%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.03 (d, J = 2.4 Hz, 2 H), 6.52 (t, J = 2.4 Hz, 1 H), 5.62 (dd, J = 7.3, 2.7 Hz, 1 H), 4.08 - 4.19 (m, 2 H), 3.93 (dd, J = 9.5, 7.2 Hz, 1 H), 3.81 (s, 6 H), 3.65 (dd, J = 9.5, 7.2 Hz, 1 H), 3.26 (dd, J = 16.5, 7.3 Hz, 1 H), 2.96 (dd, J = 16.5, 2.7 Hz, 1 H), 1.26 (t, J = 7.0 Hz, 3 H), 1.21 (t, J = 7.2 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 164.7, 162.3, 160.0 (2C), 131.6, 107.4 (2C), 104.0, 102.7, 102.5, 64.2, 59.8, 55.4 (2C), 38.5, 15.1, 14.2. **IR**: 2985.9 (w), 1701.8 (m), 1590.6 (s), 1248.4 (s), 1157.4 (s), 1082.3 (s). **HRMS** (ESI) *m/z*: [M-Na^+] calcd. for $C_{17}H_{22}O_6Na$, 345.1309; found, 345.1303.



4-7i

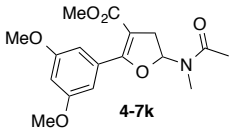
Ethyl 5-(*tert*-butoxy)-2-(3,5-dimethoxyphenyl)-4,5-dihydrofuran-3-carboxylate (4-7i). The general protocol was followed using a solution of Rh_2esp_2 (1.1 mg, 1.5 μmol) in CH_2Cl_2 (2.0 mL), *tert*-butyl vinyl ether (118 mg, 1.18 mmol), and diazo **4-9h** (359 mg, 1.29 mmol) in CH_2Cl_2 (3.5 mL). The reaction was quenched and column chromatography (15% Et_2O/hexane, R_f = 0.18) afforded **4-7i** (274 mg, 67%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.05 (d, *J* = 2.3 Hz, 2 H), 6.51 (t, *J* = 2.3 Hz, 1 H), 5.88 (dd, *J* = 7.6, 3.1 Hz, 1 H), 4.09 - 4.18 (m, 2 H), 3.80 (s, 6 H), 3.27 (dd, *J* = 16.5, 7.6 Hz, 1 H), 2.90 (dd, *J* = 16.5, 3.1 Hz, 1 H), 1.33 (s, 9 H), 1.21 (t, *J* = 7.2 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 164.9, 162.3, 159.9 (2C), 131.9, 107.4 (2C), 102.6, 102.0, 99.1, 75.7, 59.7, 55.4 (2C), 39.4, 28.8, 14.3. **IR**: 2937.8 (w), 1740.1 (w), 1662.0 (m), 1607.2 (s), 1250.0 (s), 1201.5 (s), 1025.3 (m), 800.5 (m). **HRMS** (ESI) *m/z*: [M-Na^+] calcd. for $C_{19}H_{26}O_6Na$, 373.1622; found, 373.1617.



4-7j

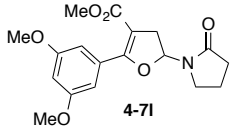
Ethyl 2-(3,5-dimethoxyphenyl)-5-((trimethylsilyl)oxy)-4,5-dihydrofuran-3-carboxylate (4-7j). The general protocol was followed using a solution of Rh_2esp_2 (1.0 mg, 1.3 μmol) in CH_2Cl_2 (2.0 mL), vinyloxy-trimethylsilane (136 mg, 1.17 mmol), and diazo **4-9h** (359 mg, 1.29 mmol) in CH_2Cl_2 (3.5 mL). The reaction was quenched and column chromatography (15% Et_2O/hexane, R_f = 0.23) afforded **4-7j** (192 mg, 45%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.05 (d, *J* = 2.4 Hz, 2 H), 6.52 (t, *J* = 2.4 Hz, 1 H), 5.92 (dd, *J* = 7.0, 2.4 Hz, 1 H), 4.12 - 4.19 (m, 2 H), 3.80 (s, 6 H), 3.26 (dd, *J* = 16.5, 7.0 Hz, 1 H), 2.93 (dd, *J* = 16.5,

2.4 Hz, 1 H), 1.22 (t, J = 7.0 Hz, 3 H), 0.23 (s, 9 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 164.9, 161.9, 160.0 (2C), 131.6, 107.3 (2C), 102.9, 102.2, 98.8, 59.8, 55.4 (2C), 41.0, 14.3, 0.2. **IR**: 2938.9 (w). 2839.9 (w), 1735.5 (w), 1661.4 (m), 1606.8 (s), 1443.0 (m), 1333.1 (m), 1249.6 (s), 1201.4 (s). **HRMS** (ESI) *m/z*: [M-Na^+] calcd. for $C_{18}H_{26}O_6NaSi$, 389.1391; found, 389.1385.



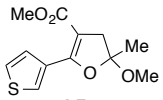
4-7k

Methyl 2-(3,5-dimethoxyphenyl)-5-(*N*-methylacetamido)-4,5-dihydrofuran-3-carboxylate (4-7k). The general protocol was followed using a solution of Rh_2esp_2 (2.2 mg, 2.9 μmol) in CH_2Cl_2 (2.0 mL), *N*-methyl-*N*-vinylacetamide (139 mg, 1.40 mmol), and diazo **4-9k** (405 mg, 1.53 mmol) in CH_2Cl_2 (4.9 mL). The reaction was quenched and column chromatography (50% EtOAc/hexane, R_f = 0.14) afforded **4-7k** (407 mg, 87%) as a white solid (mp: 142-144 °C). *Mixture of rotamers.* **^{1}H NMR** (500 MHz, $CDCl_3$, 60 °C): δ 7.04 (bs, 2.50), 6.55 (t, J = 2.3 Hz, 1.00), 6.14 - 6.47 (bs, 0.50), 3.81 (s, 6.00), 3.70 (s, 3.00), 3.31 - 3.42 (m, 1.00), 2.94 (bs, 4.00), 2.06 - 2.36 (bs, 3.00). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.3, 170.3, 164.9, 164.6, 163.9, 163.6, 160.1 (2C), 130.6, 130.4, 107.2 (2C), 103.4, 101.6, 101.5, 88.5, 83.4, 55.5 (2C), 51.3, 51.2, 34.9, 34.5, 29.1, 26.3, 22.2, 21.7. **IR**: 3004.3 (w), 2951.0 (w), 2840.3 (w), 1668.6 (s), 1588.1 (s), 1426.9 (m), 1247.3 (s), 1156.5 (s), 1091.5 (s). **HRMS** (ESI) *m/z*: [M-Na^+] calcd. for $C_{17}H_{21}NO_6Na$, 358.1261; found, 358.1262.



4-7l

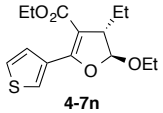
Methyl 2-(3,5-dimethoxyphenyl)-5-(2-oxopyrrolidin-1-yl)-4,5-dihydrofuran-3-carboxylate (4-7l). The general protocol was followed using a solution of Rh_2esp_2 (2.2 mg, 2.9 μmol) in CH_2Cl_2 (2.0 mL), 1-vinyl-2-pyrrolidinone (119 mg, 1.07 mmol), and diazo **4-9k** (303 mg, 1.15 mmol) in CH_2Cl_2 (3.2 mL). The reaction was quenched and column chromatography (50% EtOAc/hexane, R_f = 0.12) afforded **4-7l** (254 mg, 68%) as a white solid (mp: 124-126 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.02 (d, J = 2.1 Hz, 2 H), 6.57 (dd, J = 10.1, 4.9 Hz, 1 H), 6.50 - 6.54 (m, 1 H), 3.79 (s, 6 H), 3.68 (s, 3 H), 3.40 - 3.48 (m, 1 H), 3.30 - 3.39 (m, 2 H), 2.92 (dd, J = 16.5, 4.9 Hz, 1 H), 2.42 (t, J = 8.1 Hz, 2 H), 1.98 - 2.10 (m, 2 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.4, 164.8, 163.4, 160.0 (2C), 130.4, 107.1 (2C), 103.3, 101.1, 81.6, 55.4 (2C), 51.2, 41.2, 34.2, 31.0, 17.7. **IR**: 2948.4 (w), 2839.2 (w), 1695.9 (s), 1588.7 (s), 1457.6 (m), 1425.0 (m), 1248.4 (m), 1204.1 (s), 1156.0 (s), 1090.3 (m), 1055.4 (m), 1022.5 (m). **HRMS** (ESI) *m/z*: [M-Na^+] calcd. for $C_{18}H_{21}NO_6Na$, 370.1261; found, 370.1260.



4-7m

Methyl 5-methoxy-5-methyl-2-(thiophen-3-yl)-4,5-dihydrofuran-3-carboxylate (4-7m). The general protocol was followed using a solution of Rh_2esp_2 (1.8 mg, 2.4 μmol) in CH_2Cl_2 (2.0 mL), 2-methoxypropene (131 mg, 1.82 mmol), and diazo **4-9m** (522 mg, 2.48 mmol) in CH_2Cl_2 (9.0 mL). The reaction was quenched and column chromatography (10% Et_2O/hexane, R_f = 0.27) afforded **4-7m** (286 mg, 65%) as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.46 (dd, J = 3.1, 1.2 Hz, 1 H), 7.77 (dd, J = 5.1, 1.2 Hz, 1 H), 7.29 (dd, J = 5.1, 3.1 Hz, 1 H), 3.73 (s, 3 H), 3.34 (s, 3 H), 3.14 (d, J = 18.0 Hz, 1 H), 3.00 (d, J = 18.0 Hz,

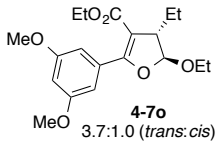
1 H), 1.65 (s, 3 H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.3, 158.2, 130.5, 130.4, 128.3, 124.5, 109.6, 100.6, 51.1, 49.9, 41.0, 25.0. **IR**: 3123.1 (w), 2995.1 (w), 2946.3 (w), 2822.2 (w), 1697.2 (s), 1612.2 (s), 1262.4 (m), 1110.2 (s), 1046.0 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{12}H_{14}O_4S$, 254.0613; found, 254.0622.



4-7n
2.8:1.0 (*trans*:*cis*)

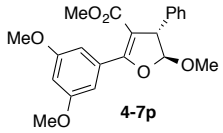
Ethyl 5-ethoxy-4-ethyl-2-(thiophen-3-yl)-4,5-dihydrofuran-3-carboxylate (4-7n). The general protocol was followed using a solution of Rh_2esp_2 (1.9 mg, 1.5 μmol) in CH_2Cl_2 (2.0 mL), 1-butenyl ethyl ether (662 mg, 6.61 mmol), and diazo **4-9d** (524 mg, 2.34 mmol) in CH_2Cl_2 (4.75 mL). The reaction was quenched and column chromatography (5% Et_2O/hexane, R_f = 0.24) afforded **4-7n** (141 mg, 21%) as a light yellow oil. *Diastereomeric mixture*: 2.8:1 (*trans*:*cis* ratio). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.38 (dd, *J* = 3.1, 1.2 Hz, 0.36, minor), 8.22 (dd, *J* = 3.1, 1.2 Hz, 1.00, major), 7.72 (ddd, *J* = 5.1, 1.2, 0.6 Hz, 0.36, minor), 7.59 - 7.64 (m, 1.00, major), 7.20 - 7.27 (m, 1.36, major + minor), 5.60 (d, *J* = 7.3 Hz, 1.00, major), 5.20 (dd, *J* = 1.7, 0.5 Hz, 0.36, minor), 4.08 - 4.27 (m, 2.72, major + minor), 3.83 - 3.99 (m, 1.36, major + minor), 3.54 - 3.70 (m, 1.36, major + minor), 3.24 (ddd, *J* = 9.2, 7.3, 3.7 Hz, 1.00, major), 3.03 - 3.10 (m, 0.36, minor), 1.67 - 1.93 (m, 2.36, major + minor), 1.39 - 1.57 (m, 0.36, minor), 1.19 - 1.30 (m, 8.16, major + minor), 0.88 - 1.00 (m, 4.08, major + minor). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.3, 165.0, 157.8, 157.6, 131.1, 131.0, 130.3, 129.7, 128.5, 128.4, 124.3, 124.2, 108.1, 106.3, 105.5, 105.3, 65.4, 64.0, 59.7, 59.7, 51.4, 48.2, 24.3, 19.8, 15.2, 15.1, 14.3, 14.3, 12.5, 10.6. **IR**: 3106.7 (w), 2965.9 (w), 2934.8 (w), 2877.7 (w), 1723.5 (m), 1670.9 (s), 1508.3 (m), 1412.9 (m), 1226.3 (m), 1174.1

(m), 1068.9 (m), 788.1 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{15}H_{20}O_4S$, 296.1082; found, 296.1086.



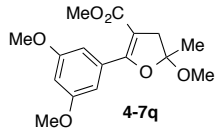
4-7o
3.7:1.0 (*trans*:*cis*)

Ethyl 2-(3,5-dimethoxyphenyl)-5-ethoxy-4-ethyl-4,5-dihydrofuran-3-carboxylate (4-7o). The general protocol was followed using a solution of Rh_2esp_2 (1.2 mg, 1.6 μmol) in CH_2Cl_2 (2.0 mL), 1-butenyl ethyl ether (229 mg, 2.29 mmol), and diazo **4-9h** (359 mg, 1.29 mmol) in CH_2Cl_2 (3.5 mL). The reaction was quenched and column chromatography (10% Et_2O/hexane, R_f = 0.13) afforded **4-7o** (206 mg, 46%) as a colorless oil. *Diastereomeric mixture*: 3.7:1 (*trans*:*cis* ratio). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.99 (d, *J* = 2.1 Hz, 0.54, minor), 6.86 (d, *J* = 2.1 Hz, 2.00, major), 6.52 (t, *J* = 2.1 Hz, 0.27, minor), 6.50 (t, *J* = 2.1 Hz, 1.00 major), 5.63 (d, *J* = 7.3 Hz, 1.00, major), 5.24 (d, *J* = 1.8 Hz, 0.27, minor), 4.06 - 4.18 (m, 2.54, major + minor), 3.89 - 3.97 (m, 1.27, major + minor), 3.81 (s, 1.62, minor), 3.80 (s, 6.00, major), 3.60 - 3.71 (m, 1.27, major + minor), 3.24 - 3.31 (m, 1.00, major), 3.07 - 3.12 (m, 0.27, minor), 1.73 - 1.96 (m, 2.27, major + minor), 1.50 - 1.61 (m, 0.27, minor), 1.24 - 1.30 (m, 3.81, major + minor), 1.14 - 1.23 (m, 3.81, major + minor), 0.94 - 1.03 (m, 3.81, major + minor). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.2, 164.7, 162.5, 162.2, 160.0 (2C), 132.2, 131.9, 108.5, 107.6, 107.2 (2C), 106.9, 106.8, 106.5, 102.7, 102.4, 65.4, 64.2, 59.6, 55.4 (2C), 55.4, 51.5, 48.5, 24.3, 19.5, 15.2, 15.1, 14.2, 14.1, 12.5, 10.5. **IR**: 2966.6 (w), 2839.1 (w), 1727.0 (w), 1592.3 (s), 1203.0 (s), 1153.3 (s). **HRMS** (ESI) *m/z*: [M-Na^+] calcd. for $C_{19}H_{26}O_6Na$, 373.1622; found, 373.1620.



4-7p

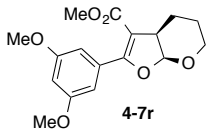
Methyl 2-(3,5-dimethoxyphenyl)-5-methoxy-4-phenyl-4,5-dihydrofuran-3-carboxylate (4-7p). The general protocol was followed using a solution of Rh_2esp_2 (1.6 mg, 2.1 μmol) in CH_2Cl_2 (2.0 mL), (2-methoxyvinyl)benzene **4-10p** (231 mg, 1.72 mmol), and diazo **4-9k** (509 mg, 1.93 mmol) in CH_2Cl_2 (4.9 mL). The reaction was quenched and column chromatography (20% Et_2O/hexane, R_f = 0.18) afforded **4-7p** (306 mg, 48%) as a light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.29 - 7.34 (m, 2 H), 7.25 - 7.28 (m, 3 H), 7.08 (d, J = 2.4 Hz, 2 H), 6.58 (t, J = 2.3 Hz, 1 H), 5.72 (d, J = 7.9 Hz, 1 H), 4.59 (d, J = 7.6 Hz, 1 H), 3.84 (m, 6 H), 3.48 (s, 3 H), 3.45 (s, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 164.9, 163.4, 160.1 (2C), 136.4, 131.3, 129.1 (2C), 127.8 (2C), 127.0, 107.6, 107.3 (2C), 107.2, 103.2, 57.4, 55.5 (2C), 53.6, 51.0. **IR**: 3018.4 (w), 2949.3 (w), 2839.8 (w), 1734.2 (m), 1596.4 (s), 1454.8 (m), 1204.3 (s), 1155.8 (m), 1066.4 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{21}H_{22}O_6$, 370.1416; found, 370.1404.



4-7q

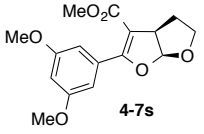
Methyl 2-(3,5-dimethoxyphenyl)-5-methoxy-5-methyl-4,5-dihydrofuran-3-carboxylate (4-7q). The general protocol was followed using a solution of Rh_2esp_2 (1.3 mg, 1.7 μmol) in CH_2Cl_2 (2.0 mL), 2-methoxypropene (101 mg, 1.40 mmol), and diazo **4-9k** (401 mg, 1.52 mmol) in CH_2Cl_2 (5.5 mL). The reaction was quenched and column chromatography (25% Et_2O/hexane, R_f = 0.24) afforded **4-7q** (387 mg, 90%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.04 (d, J = 2.4 Hz, 2 H), 6.54 (t, J = 2.4 Hz, 1 H), 3.81 (s, 6 H), 3.68 (s, 3 H), 3.37

(s, 3 H), 3.12 - 3.19 (m, 1 H), 3.00 - 3.06 (m, 1 H), 1.65 (s, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.1, 162.7, 160.1 (2C), 131.3, 109.8, 107.3 (2C), 103.0, 102.2, 55.5 (2C), 51.1, 50.0, 41.4, 24.8. **IR**: 2999.2 (w), 2947.2 (w), 2837.1 (w), 1705.6 (m), 1588.8 (s), 1456.8 (m), 1204.4 (s), 1156.8 (s), 1113.1 (s), 1041.5 (s), 855.1 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{16}H_{20}O_6$, 308.1260; found, 308.1265.



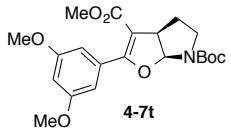
4-7r

Methyl 2-(3,5-dimethoxyphenyl)-3a,5,6,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-3-carboxylate (4-7r). The general protocol was followed using a solution of Rh_2esp_2 (2.2 mg, 2.9 μmol) in CH_2Cl_2 (2.0 mL), 3,4-dihydro-2*H*-pyran (117 mg, 1.39 mmol), and diazo **4-9k** (401 mg, 1.52 mmol) in CH_2Cl_2 (4.9 mL). The reaction was quenched and column chromatography (30% Et_2O/hexane, R_f = 0.31) afforded **4-7r** (59 mg, 13%) as a light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.00 (d, *J* = 2.4 Hz, 2 H), 6.53 (t, *J* = 2.4 Hz, 1 H), 5.90 (d, *J* = 7.3 Hz, 1 H), 3.83 - 3.90 (m, 2 H), 3.80 (s, 6 H), 3.68 (s, 3 H), 3.09 - 3.17 (m, 1 H), 2.10 - 2.17 (m, 1 H), 1.64 - 1.75 (m, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.3, 163.6, 160.0 (2C), 131.3, 107.9, 107.1 (2C), 103.9, 103.4, 61.3, 55.4 (2C), 51.0, 39.4, 23.4, 20.3. **IR**: 2950.7 (m), 2841.5 (w), 1685.4 (m), 1585.8 (s), 1454.4 (m), 1425.3 (m), 1204.1 (s), 1153.6 (s), 1087.2 (s), 1057.3 (s), 924.2 (m), 850.9 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{17}H_{20}O_6$, 320.1260; found, 320.1261.



4-7s

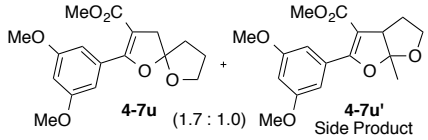
Methyl 2-(3,5-dimethoxyphenyl)-3a,4,5,6a-tetrahydrofuro[2,3-*b*]furan-3-carboxylate (4-7s). The general protocol was followed using a solution of Rh_2esp_2 (2.2 mg, 2.9 μmol) in CH_2Cl_2 (4.0 mL), 2,3-dihydrofuran (170 mg, 2.43 mmol), and diazo **4-9k** (707 mg, 2.68 mmol) in CH_2Cl_2 (8.0 mL). The reaction was quenched and column chromatography (30% Et_2O/hexane, R_f = 0.24) afforded **4-7s** (304 mg, 41%) as a light yellow solid (mp: 79-80 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.98 (d, *J* = 2.1 Hz, 2 H), 6.54 (t, *J* = 2.1 Hz, 1 H), 6.21 (d, *J* = 6.4 Hz, 1 H), 4.08 - 4.13 (m, 1 H), 3.94 - 4.00 (m, 1 H), 3.79 - 3.84 (m, 7 H), 3.70 (s, 3 H), 2.07 - 2.26 (m, 2 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.2, 164.9, 160.0 (2C), 130.9, 108.9, 107.2 (2C), 103.9, 103.4, 67.0, 55.5 (2C), 51.1, 48.8, 32.2. **IR**: 2990.4 (w), 2951.0 (m), 2894.5 (w), 2839.9 (w), 1684.8 (m), 1586.7 (s), 1425.4 (m), 1237.0 (m), 1155.2 (s), 1054.5 (s), 926.2 (m), 836.7 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{16}H_{18}O_6$, 306.1103; found, 306.1096.



4-7t

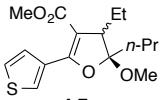
6-(*tert*-butyl) 3-methyl 2-(3,5-dimethoxyphenyl)-3a,4,5,6a-tetrahydro-6*H*-furo[2,3-*b*]pyrrole-3,6-dicarboxylate (4-7t). The general protocol was followed using a solution of Rh_2esp_2 (3.5 mg, 4.6 μmol) in CH_2Cl_2 (4.0 mL), *N*-Boc-2,3-dihydro-1*H*-pyrrole (343 mg, 2.03 mmol), and diazo **4-9k** (1.19 g, 4.50 mmol) in CH_2Cl_2 (7.2 mL). The reaction was quenched and column chromatography (30% Et_2O/hexane, R_f = 0.19) afforded **4-7t** (196 mg, 24%) as a light yellow oil. *Mixture of rotamers*. **^{1}H NMR** (500 MHz, $CDCl_3$, 50 ^oC): δ 6.93 (br. s., 2 H), 6.48 - 6.56 (m, 1 H), 6.11 - 6.42 (m, 1 H), 3.94 - 4.11 (m, 1 H), 3.79 (s, 6 H), 3.77 (m, 1 H), 3.68 (s, 3 H), 3.31 (dd, *J* = 8.7, 1.7 Hz, 1 H), 2.17 (m, 2 H), 1.43 - 1.55 (s, 9

H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 164.9, 160.0, 107.3, 103.9, 103.2, 102.8, 100.5, 97.8, 93.0, 92.6, 80.7, 55.4, 53.4, 51.8, 51.1, 48.6, 47.6, 44.3, 43.7, 31.0, 29.9, 28.6, 28.4, 28.3. **IR**: 3002.2 (w), 2974.7 (w), 2888.8 (w), 1705.0 (s), 1589.8 (s), 1393.7 (s), 1157.5 (s), 1058.6 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{21}H_{27}NO_7$, 405.1788; found, 405.1783.



Methyl 2-(3,5-dimethoxyphenyl)-1,6-dioxaspiro[4.4]non-2-ene-3-carboxylate (4-7u). The general protocol was followed using a solution of Rh_2esp_2 (1.4 mg, 1.8 μmol) in CH_2Cl_2 (2.0 mL), 2-methylenetetrahydrofuran **4-10u** (124 mg, 1.47 mmol), and diazo **4-9k** (401 mg, 1.52 mmol) in CH_2Cl_2 (4.9 mL). The reaction was quenched and column chromatography (25% Et_2O/hexane, R_f = 0.23) afforded **4-7u** along with **4-7u'** (216 mg, 46%) as a yellow oil. *Mixture of inseparable compounds*: 1.7:1 (**4-7u:4-7u'** ratio). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.98 (d, *J* = 2.4 Hz, 2.00, major), 6.97 (d, *J* = 2.4 Hz, 1.18, minor), 6.53 (t, *J* = 2.4 Hz, 0.59, minor), 6.51 (t, *J* = 2.4 Hz, 1.00, major), 4.18 - 4.01 (m, 3.18, major + minor), 3.79 - 3.82 (m, 10.13, major + minor), 3.68 (s, 1.77, minor), 3.66 (s, 3.00, major), 3.21 (s, 2.00, major), 2.37 - 2.42 (m, 1.18, minor), 1.97 - 2.29 (m, 4.00, major), 1.68 (s, 1.77, minor). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.1 (major), 164.7 (minor), 162.4 (major), 160.9 (minor), 160.0 (2C, major), 159.9 (2C, minor), 131.7 (major), 131.1 (minor), 117.8 (minor), 116.3 (major), 107.3 (2C, major), 107.2 (2C, minor), 104.0 (minor), 103.2 (minor), 102.8 (major), 101.8 (major), 68.8 (major), 67.6 (minor), 55.5 (2C, major), 55.4 (2C, minor), 53.4 (minor), 52.4 (minor), 51.0 (major), 39.9 (major), 36.7 (major), 31.0 (minor), 23.8 (major), 23.8 (minor). **IR**: 2946.5 (w), 2839.0 (w), 1774.7 (m), 1684.8 (m), 1588.3 (s), 1456.9 (m), 1426.2 (m), 1204.0 (s),

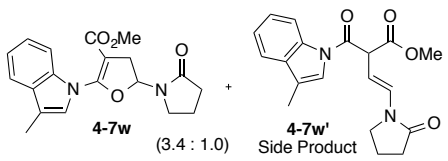
1155.2 (s), 1054.0 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{17}H_{20}O_6$, 320.1260; found, 320.1252.



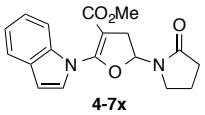
4-7v
2.1:1.0 *dr*

Methyl 4-ethyl-5-methoxy-5-propyl-2-(thiophen-3-yl)-4,5-dihydrofuran-3-carboxylate (4-7v). A protocol developed by Corey was followed.[7] A pre-dried round bottom flask was charged with anhydrous $Mn(OAc)_3$ (1.06 g, 2.54 mmol), which was dissolved at 40 °C using AcOH (5.5 mL). Then, the mixture was allowed to reach room temp before the addition of 4-methoxyhept-3-ene **4-10v** (752 mg, 5.86 mmol) and β-ketoester **4-11m** (283 mg, 1.54 mmol). The reaction mixture was stirred at room temp for 3 hrs before removing AcOH under reduced pressure. At this point, the crude was diluted with saturated $NaHCO_3$, extracted with EtOAc (2x), dried over Na_2SO_4 and purified via column chromatography [5% Et_2O/hexane, R_f = 0.31 (major diastereomer), 0.20 (minor diastereomer)] to afford **4-7v** (329 mg, 69%) as a colorless oil. *Diastereomeric mixture*: 2.1:1.0. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.40 (dd, *J* = 3.1, 1.2 Hz, 0.48, minor), 8.27 (dd, *J* = 3.1, 1.2 Hz, 1.00, major), 7.75 (dd, *J* = 5.2, 1.2 Hz, 0.48, minor), 7.65 (dd, *J* = 5.2, 1.2 Hz, 1.00, major), 7.24 - 7.31 (m, 1.48, major + minor), 3.72 (s, 4.43, major + minor), 3.42 (s, 3.00, major), 3.30 (s, 1.43, minor), 3.15 (dd, *J* = 7.9, 3.7 Hz, 1.00, major), 3.10 (t, *J* = 5.8 Hz, 0.48, minor), 2.00 - 2.10 (m, 0.48, minor), 1.69 - 1.93 (m, 4.96, major + minor), 1.33 - 1.58 (m, 3.44, major + minor), 0.94 - 1.02 (m, 7.43, major + minor), 0.90 (t, *J* = 7.5 Hz, 1.43, minor). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.8, 165.7, 157.2, 157.2, 131.0, 130.9, 130.3, 129.8, 128.5, 128.4, 124.5, 124.3, 112.5, 112.4, 106.9, 105.6, 51.0, 50.9, 50.9, 50.7, 50.4, 49.2, 38.0, 32.9, 23.0, 21.1, 17.4, 16.5, 14.3, 14.2,

12.7, 10.9. **IR**: 2982.0 (w), 1753.9 (s), 1371.4 (m), 1236.4 (s), 1045.4 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{16}H_{22}O_4S$, 310.1239; found, 310.1242.

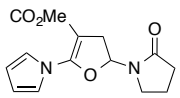


Methyl 2-(3-methyl-1*H*-indol-1-yl)-5-(2-oxopyrrolidin-1-yl)-4,5-dihydrofuran-3-carboxylate (4-7w). The general protocol was followed using a solution of Rh_2esp_2 (1.6 mg, 2.1 μmol) in CH_2Cl_2 (2.0 mL), 1-vinyl-2-pyrrolidinone (117 mg, 1.05 mmol), and diazo **4-9w** (312 mg, 1.21 mmol) in CH_2Cl_2 (3.3 mL). The reaction was quenched and column chromatography (50% EtOAc/hexane, R_f = 0.18) afforded **4-7w** along with **4-7w'** (72.1 mg, 20%) as a yellow oil. *Mixture of inseparable compounds*: 3.4:1.0 (**4-7w**:**4-7w**' ratio). **^{1}H NMR** (500 MHz, $CDCl_3$) **Only major product 4-7w reported**: δ 7.55 - 7.56 (m, 2 H), 7.52 - 7.54 (m, 1 H), 7.19 - 7.25 (m, 2 H), 6.67 (dd, *J* = 9.8, 4.6 Hz, 1 H), 3.69 (s, 3 H), 3.38 - 3.55 (m, 3 H), 2.96 - 3.04 (m, 1 H), 2.44 - 2.53 (m, 2 H), 2.28 (s, 3 H), 2.06 - 2.17 (m, 2 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.7, 164.2, 155.7, 135.9, 130.6, 125.2, 123.5, 122.0, 119.0, 115.7, 114.2, 85.9, 81.5, 53.2, 41.6, 32.5, 31.0, 18.0, 9.6. **IR**: 2953.0 (w), 1743.7 (m), 1689.6 (s), 1450.5 (m), 1379.1 (m), 1211.2 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{19}H_{20}N_2O_4$, 340.1423; found, 340.1431.



Methyl 2-(1*H*-indol-1-yl)-5-(2-oxopyrrolidin-1-yl)-4,5-dihydrofuran-3-carboxylate (4-7x). The general protocol was followed using a solution of Rh_2esp_2 (1.9 mg, 2.5 μmol) in

CH_2Cl_2 (2.0 mL), 1-vinyl-2-pyrrolidinone (134 mg, 1.21 mmol), and diazo **4-9x** (306 mg, 1.26 mmol) in CH_2Cl_2 (3.6 mL). The reaction was quenched and column chromatography (50% EtOAc/hexane, R_f = 0.15) afforded **4-7x** (271 mg, 69%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 3.7 Hz, 1 H), 7.55 - 7.58 (m, 2 H), 7.16 - 7.25 (m, 2 H), 6.69 (dd, *J* = 9.6, 5.0 Hz, 1 H), 6.63 (dd, *J* = 3.7, 0.8 Hz, 1 H), 3.68 (s, 3 H), 3.37 - 3.56 (m, 3 H), 3.02 (dd, *J* = 15.6, 5.0 Hz, 1 H), 2.43 - 2.51 (m, 2 H), 2.04 - 2.14 (m, 2 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.6, 164.0, 155.5, 135.5, 129.5, 128.3, 123.4, 122.2, 121.0, 113.8, 106.2, 87.3, 81.6, 51.1, 41.5, 32.3, 30.9, 17.9. **IR**: 2951.9 (w), 1740.4 (m), 1684.2 (s), 1451.2 (s), 1204.2 (s), 732.1 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{18}H_{18}N_2O_4$, 326.1267; found, 326.1263.



4-7z

Methyl 5-(2-oxopyrrolidin-1-yl)-2-(1*H*-pyrrol-1-yl)-4,5-dihydrofuran-3-carboxylate (4-7z). The general protocol was followed using a solution of Rh_2esp_2 (2.2 mg, 2.9 μmol) in CH_2Cl_2 (2.0 mL), 1-vinyl-2-pyrrolidinone (155 mg, 1.39 mmol), and diazo **4-9z** (307 mg, 1.59 mmol) in CH_2Cl_2 (5.0 mL). The reaction was quenched and column chromatography (50% EtOAc/hexane, R_f = 0.21) afforded **4-7z** (198 mg, 51%) as a light yellow solid (mp: 125-126 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.53 - 7.60 (m, 2 H), 6.56 (dd, *J* = 9.8, 4.9 Hz, 1 H), 6.24 - 6.27 (m, 2 H), 3.72 (s, 3 H), 3.44 - 3.51 (m, 1 H), 3.33 - 3.43 (m, 2 H), 2.97 (dd, *J* = 15.6, 4.9 Hz, 1 H), 2.41 - 2.49 (m, 2 H), 2.00 - 2.12 (m, 2 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.7, 164.2, 154.1, 121.5 (2C), 111.2 (2C), 84.4, 81.2, 51.2, 41.3, 33.3, 30.9,

17.8. **IR**: 2947.6 (w), 1703.3 (s), 1624.4 (m), 1406.3 (m), 1378.5 (m), 1250.8 (m), 1121.6 (m), 1073.15 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{14}H_{16}N_2O_4$, 276.1110; found, 276.1107.

c. Reaction optimizations (tri-substituted DHF)

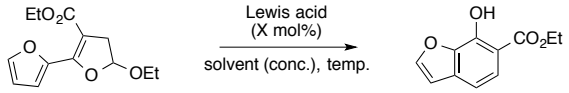
Procedure for Catalyst Screening: To a flask charged with a stir bar and the appropriate loading of the relevant Lewis acid was added a solution of DHF **4-7a** (1.0 equiv) in CH_2Cl_2 (0.2 M) at room temperature. The reaction mixture was either kept at room temperature or refluxed. Upon complete disappearance of DHF **4-7a** on TLC, the reaction was quenched with water. The mixture was extracted with CH_2Cl_2, dried with Na_2SO_4, and purification via column chromatography provided the *o*-phenolic ester product.

Procedure for Optimization of Catalyst Loading: To a flask charged with a stir bar and the appropriate $Al(OTf)_3$ loading (5-20 mol%) was added a solution of DHF **4-7a** (1.0 equiv.) in CH_2Cl_2 (0.2 M) at room temperature and then the mixture was either kept at room temperature or heated. Upon complete disappearance of DHF **4-7a** on TLC, the reaction was quenched with water. The mixture was extracted with CH_2Cl_2, dried with Na_2SO_4, and purification via column chromatography provided the *o*-phenolic ester product.

Procedure for Solvent Screening: To a flask charged with a stir bar and 5 mol% $Al(OTf)_3$ was added a solution of DHF **4-7a** (1.0 equiv) in the appropriate solvent (PhMe, 1,2-DCE, or MeCN) (0.2 M) at room temperature. The reaction mixture was heated to the indicated temperature and upon complete disappearance of DHF **4-7a** on TLC, the reaction was

quenched with water. The mixture was extracted with CH_2Cl_2, dried with Na_2SO_4, and purification via column chromatography provided the *o*-phenolic ester product.

Table S4-1. Full optimization data of the cascade reaction.



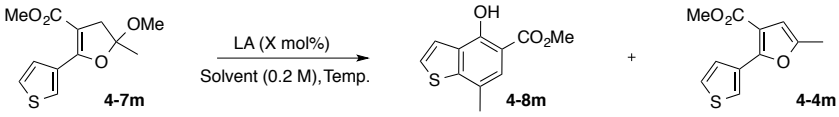
4-7a **4-8a**

Lewis Acid	Loading	Solvent, Conc.	Temp. (°C)	Time (h)	% Yield
$In(OTf)_3$	5 mol %	DCM, 0.2 M	23	45	5
$Ga(OTf)_3$	5 mol %	DCM, 0.2 M	23	9.5	16
$Ga(OTf)_3$	5 mol %	DCM, 0.2 M	40	1.0	22
$Sc(OTf)_3$	5 mol %	DCM, 0.2 M	23	9.5	Decomp.
$Yb(OTf)_3$	5 mol %	DCM, 0.2 M	23	20	NR
$Cu(OTf)_2$	5 mol %	DCM, 0.2 M	23	45	Decomp.
$Al(OTf)_3$	5 mol %	DCM, 0.2 M	23	45	19
$Al(OTf)_3$	5 mol %	DCM, 0.2 M	40	6.5	35
$Al(OTf)_3$	5 mol %	Toluene, 0.2 M	35	27	13
$Al(OTf)_3$	5 mol %	Toluene, 0.2 M	50	19	28
$Al(OTf)_3$	5 mol %	Toluene, 0.2 M	70	2.5	41
$Al(OTf)_3$	10 mol %	Toluene, 0.2 M	70	2.5	39
$Al(OTf)_3$	15 mol %	Toluene, 0.2 M	70	2.5	43
$Al(OTf)_3$	20 mol %	Toluene, 0.2 M	70	1.0	33
$Al(OTf)_3$	**5 mol %**	**Toluene, 0.2 M**	**85**	**1.0**	**46, 42 (2nd)**
$Al(OTf)_3$	5 mol %	Toluene, 0.2 M	110	1.0	40
$Al(OTf)_3$	10 mol %	Toluene, 0.2 M	85	0.67	40
$Al(OTf)_3$	15 mol %	Toluene, 0.2 M	85	0.5	37
$Al(OTf)_3$	5 mol %	Toluene, 0.1 M	85	1.0	31
$Al(OTf)_3$	5 mol %	Toluene, 0.15 M	85	1.0	44

d. Reaction optimizations (tetra-substituted DHF)

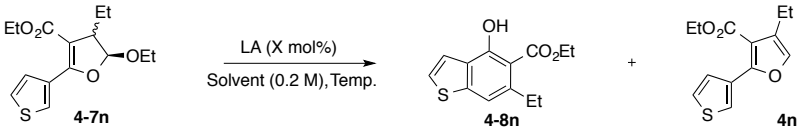
A similar optimization procedure as detailed above was followed but adding a drop of water to the reaction mixture prior heating [only when using $Al(OTf)_3$].

Table S4-2. Full optimization data for tetra-substituted DHF 4-7m.



Lewis Acid	Loading (mol %)	Solvent	Temp. (°C)	Time (h)	Ratio 4-8m:4-4m
$SnCl_4$	400	DCE	82	1.0	**4-4m** Only
$In(OTf)_3$	5	DCE	65	4.0	1:38
$In(OTf)_3$	5	DCM	23	4.0	1:29
$Sc(OTf)_3$	5	DCE	65	4.0	1:21
$Sc(OTf)_3$	10	DCM	23	3.0	1:10
$Sc(OTf)_3$	10	DCM	0	2.0	1:9.1
$Sc(OTf)_3$	30	DCM	23	3.0	1:9.4
$Sc(OTf)_3$	10	CH_3CN	23	2.5	1:20
$Sc(OTf)_3$	10	C_6H_6	23	2.0	1:3.4
$Sc(OTf)_3$	10	PhMe	23	2.0	1:3.5
$Ga(OTf)_3$	10	PhMe	23	2.0	1:2.4
BF_3.OEt	100	PhMe	0	4.0	**4-4m** Only
$Hg(OTf)_2$	10	PhMe	23	1.0	**4-4m** Only
$Al(OTf)_3$	10	PhMe	23	20	**4-4m** Only
$Al(OTf)_3$, Drop H_2O	5	PhMe	70	2.5	1:1.18
$Al(OTf)_3$, Drop H_2O	10	PhMe	70	2.5	1:0.26
$Al(OTf)_3$, Drop H_2O	**20**	**PhMe**	**70**	**2.0**	**1:0.16, 80% Yield**

Table S4-3. Full optimization data for tetra-substituted DHF 4-4n.

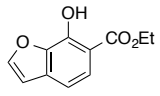


Lewis Acid	Loading (mol %)	Solvent	Temp. (°C)	Time (h)	Ratio 4-8n:4-4n
$In(OTf)_3$	5	DCE	82	8.0	1:1.5
$Sc(OTf)_3$	5	DCE	82	0.25	1:0.79
$Al(OTf)_3$, Drop H_2O	**20**	**PhMe**	**70**	**4.0**	**4-8n only, 69% Yield**

e. Catalytic, ring-opening/cyclization/elimination cascade (4-8a to 4-8v and 4-12w to 4-12z)

General Procedure A: To a pre-dried round bottom flask charged with $Al(OTf)_3$ (5 mol %) was added the corresponding 2,3-DHF **4-7** in anhydrous toluene ($PhCH_3$, 0.2 M). The reaction was heated to 85 °C and monitored via TLC. Upon complete disappearance of the starting material, the reaction was quenched with H_2O (2 mL). The mixture was extracted with EtOAc (2x), dried with Na_2SO_4, and column chromatography provided the benzo-fused heteroaromatic.

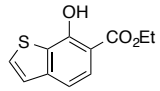
General Procedure B: To a pre-dried round bottom flask charged with $Al(OTf)_3$ (20 mol %) was added 0.5-1.0 mL of anhydrous $PhCH_3$ and a drop of water. After stirring for 15 min at room temperature, the corresponding 2,3-DHF **4-7** in anhydrous $PhCH_3$ (final concentration = 0.2 M). The reaction was heated to 70 °C and monitored via TLC. Upon complete disappearance of the starting material, the reaction was quenched with H_2O (2 mL). The mixture was extracted with EtOAc (2x), dried with Na_2SO_4, and column chromatography provided the benzo-fused heteroaromatic.



4-8a

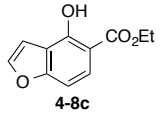
Ethyl 7-hydroxybenzofuran-6-carboxylate (4-8a). The general protocol A was followed using $Al(OTf)_3$ (7.0 mg, $1.5*10^{-2}$ mmol) and 2,3-DHF **4-7a** (74.9 mg, $2.97*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.5 mL). The reaction was quenched and column chromatography (10% Et_2O/hexane, R_f = 0.41) afforded **4-8a** (28.0 mg, 46%) as a white solid (mp: 96-98 °C). **^{1}H**

NMR (500 MHz, $CDCl_3$): δ 11.39 (s, 1 H), 7.75 (d, J = 2.1 Hz, 1 H), 7.69 (d, J = 8.2 Hz, 1 H), 7.07 (d, J = 8.2 Hz, 1 H), 6.77 (d, J = 2.1 Hz, 1 H), 4.43 (q, J = 7.0 Hz, 2 H), 1.43 (t, J = 7.0 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.9, 148.6, 147.8, 143.1, 134.2, 123.8, 111.4, 108.0, 107.3, 61.4, 14.2. **IR**: 3140.5 (w), 3004.3 (w), 2925.5 (w), 1674.7 (m), 1487.3 (m), 1364.5 (m), 1264.6 (m), 1066.1 (m), 730.9 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{11}H_{10}O_4$, 206.0579; found, 206.0571.



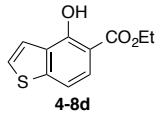
4-8b

Ethyl 7-hydroxybenzo[*b*]thiophene-6-carboxylate (4-8b). The general protocol A was followed using $Al(OTf)_3$ (9.4 mg, $2.0*10^{-2}$ mmol) and 2,3-DHF **4-7** (104 mg, $3.88*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.9 mL). The reaction was quenched and column chromatography (2% Et_2O/hexane, R_f = 0.19) afforded **4-8b** (62.9 mg, 61%) as a white solid (mp: 70-71 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.67 (s, 1 H), 7.79 (d, J = 8.5 Hz, 1 H), 7.63 (d, J = 5.2 Hz, 1 H), 7.27 - 7.36 (m, 3 H), 4.44 (q, J = 7.2 Hz, 2 H), 1.44 (t, J = 7.2 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.8, 157.8, 145.6, 131.0, 127.7, 125.2, 124.3, 114.6, 106.2, 61.4, 14.2. **IR**: 3106.9 (w), 3043.2 (w), 2979.6 (w), 2904.2 (w), 1616.3 (s), 1474.2 (s), 1374.6 (s), 1267.1 (s), 1154.1 (s), 1020.0 (s), 787.3 (s). **HRMS** (ESI) *m/z*: [M-H^+] calcd. for $C_{11}H_{11}O_3S$, 223.0423; found, 223.0419.



4-8c

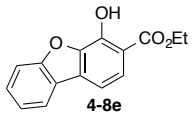
Ethyl 4-hydroxybenzofuran-5-carboxylate (4-8c). The general protocol A was followed using $Al(OTf)_3$ (8.1 mg, $1.7*10^{-2}$ mmol) and 2,3-DHF **4-7c** (85.2 mg, $3.38*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.7 mL). The reaction was quenched and column chromatography (2% Et_2O/hexane, R_f = 0.20) afforded **4-8c** (63.5 mg, 75%) as a white solid (mp: 55-56 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.57 (s, 1 H), 7.78 (d, *J* = 8.9, 1 H), 7.56 (d, *J* = 2.4 Hz, 1 H), 7.02 (d, *J* = 8.9, 1 H), 6.97 (d, *J* = 2.4, 1 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 1.43 (t, *J* = 7.2 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.8, 159.5, 157.5, 144.2, 125.9, 117.0, 106.2, 104.7, 103.7, 61.2, 14.2. **IR**: 2985.6 (w), 1663.5 (s), 1628.7 (m), 1468.6 (s), 1281.4 (s), 1178.5 (s), 1055.3 (m), 749.2 (s). **HRMS** (ESI) *m/z*: [M-H$^+$] calcd. for $C_{11}H_{11}O_4$, 207.0652; found, 207.0647.



4-8d

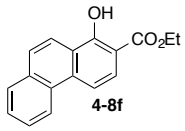
Ethyl 4-hydroxybenzo[*b*]thiophene-5-carboxylate (4-8d). The general protocol A was followed using $Al(OTf)_3$ (14.5 mg, $3.06*10^{-2}$ mmol) and 2,3-DHF **4-7d** (161 mg, $6.00*10^{-1}$ mmol) in anhydrous $PhCH_3$ (3.0 mL). The reaction was quenched and column chromatography (5% Et_2O/hexane, R_f = 0.40) afforded **4-8d** (108 mg, 81%) as a white solid (mp: 59-60 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.69 (s, 1 H), 7.75 (d, *J* = 8.5 Hz, 1 H), 7.63 (dd, *J* = 5.5, 0.6 Hz, 1 H), 7.36 (d, *J* = 5.5 Hz, 1 H), 7.34 (dd, *J* = 8.5, 0.6 Hz, 1 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 1.44 (t, *J* = 7.2 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.9, 158.3, 146.8, 129.8, 125.2, 124.6, 121.4, 113.1, 106.5, 61.3, 14.2. **IR**: 3089.1 (w), 2983.1 (w),

1659.2 (s), 1616.2 (m), 1431.6 (s), 1372.7 (s), 1334.2 (s), 1265.5 (s), 1155.8 (s), 751.7 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{11}H_{10}O_3S$, 222.0351; found, 222.0349.



4-8e

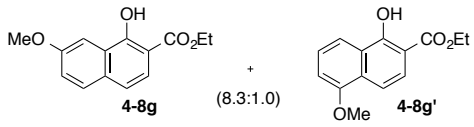
Ethyl 4-hydroxydibenzo[*b*,*d*]furan-3-carboxylate (4-8e). The general protocol A was followed using $Al(OTf)_3$ (7.2 mg, $1.5*10^{-2}$ mmol) and 2,3-DHF **4-7e** (90.0 mg, $2.98*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.5 mL). The reaction was quenched and column chromatography (2% Et_2O/hexane, R_f = 0.15) afforded **4-8e** (63.7 mg, 83%) as a white solid (mp: 123-124 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.33 - 11.41 (m, 1 H), 7.90 - 7.97 (m, 1 H), 7.76 - 7.83 (m, 1 H), 7.65 (dd, *J* = 8.2, 0.6 Hz, 1 H), 7.52 (td, *J* = 7.8, 1.2 Hz, 1 H), 7.38 - 7.44 (m, 1 H), 7.32 - 7.38 (m, 1 H), 4.40 - 4.50 (m, 2 H), 1.39 - 1.51 (m, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.5, 157.2, 148.5, 143.8, 130.5, 128.5, 126.3, 123.9, 123.7, 123.1, 121.4, 112.3, 110.6, 61.6, 14.2. **IR**: 3000.2 (w), 1680.4 (m), 1637.1 (m), 1374.0 (m), 1319.8 (s), 1285.2 (m), 746.0 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{15}H_{12}O_4$, 256.0736; found, 256.0743.



4-8f

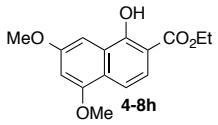
Ethyl 1-hydroxyphenanthrene-2-carboxylate (4-8f). The general protocol A was followed using $Al(OTf)_3$ (6.7 mg, $1.4*10^{-2}$ mmol) and 2,3-DHF **4-7f** (82.5 mg, $2.64*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.3 mL). The reaction was quenched and column chromatography (2% Et_2O/hexane, R_f = 0.26) afforded **4-8f** (41.8 mg, 60%) as a yellow solid (mp: 108-110 °C). **^{1}H**

NMR (500 MHz, $CDCl_3$): δ 11.94 (s, 1 H), 8.61 - 8.66 (m, 1 H), 8.34 (d, *J* = 9.5 Hz, 1 H), 8.11 (d, *J* = 8.9 Hz, 1 H), 7.98 (d, *J* = 8.9 Hz, 1 H), 7.90 - 7.94 (m, 1 H), 7.80 (d, *J* = 8.9 Hz, 1 H), 7.63 - 7.69 (m, 2 H), 4.48 (q, *J* = 7.2 Hz, 2 H), 1.48 (t, *J* = 7.2 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.8, 160.2, 135.2, 133.4, 129.5, 128.6, 127.7, 126.7, 126.5, 125.6, 123.6, 122.4, 120.8, 113.3, 107.5, 61.5, 14.3. **IR**: 3061.6 (w), 3039.7 (w), 2981.9 (m), 2927.5 (w), 2905.1 (w), 1659.9 (s), 1626.3 (m), 1466.9 (m), 1332.8 (s), 1259.2 (s), 1178.1 (s), 1073.1 (m), 1035.5 (m), 795.4 (s), 747.3 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{17}H_{14}O_3$, 266.0943; found, 266.0941.



Ethyl 1-hydroxy-7-methoxy-2-naphthoate (4-8g). The general protocol A was followed using $Al(OTf)_3$ (6.6 mg, $1.4*10^{-2}$ mmol) and 2,3-DHF **4-7g** (76.3 mg, $2.61*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.3 mL). The reaction was quenched and column chromatography (2% Et_2O/hexane, R_f = 0.12) afforded **4-8g** along with **4-8g'** (51.9 mg, 81%) as a white solid (mp: 59-60 °C). *Regioisomer mixture* 8.3:1.0. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.04 (s, 1.00, major), 12.02 (s, 0.12, minor), 7.96 - 8.02 (m, 0.12, minor), 7.74 - 7.80 (m, 0.12 minor), 7.70 (d, *J* = 0.6 Hz, 0.12, minor), 7.68 (d, *J* = 2.4 Hz, 1.00, major), 7.66 - 7.67 (m, 1.00, major), 7.65 (d, *J* = 3.7 Hz, 1.00, major), 7.40 - 7.45 (m, 0.12 minor), 7.23 - 7.27 (m, 1.00, major), 7.21 (d, *J* = 8.9 Hz, 1.00, major), 6.93 - 6.96 (m, 0.12, minor), 4.45 (q, *J* = 7.2 Hz, 2.24, major + minor), 3.98 (s, 0.36, minor), 3.96 (s, 3.00, major), 1.45 (t, *J* = 7.2 Hz, 3.36, major + minor). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.2, 171.1, 160.5, 159.7, 157.7, 155.0, 132.4, 132.3 129.0, 128.9, 125.7, 125.6, 123.5, 121.9, 121.8, 118.2, 115.7, 112.5, 107.4, 106.3,

106.1, 101.8, 61.3, 61.3, 55.5, 55.4, 14.2, 14.2. **IR**: 3064.2 (w), 2980.9 (w), 2829.2 (w), 1655.2 (s), 1608.5 (s), 1443.5 (m), 1327.9 (s), 1251.8 (s), 1223.9 (s), 1175.5 (s), 1024.8 (s), 715.9 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{14}H_{14}O_4$, 246.0892; found, 246.0890.



4-8h

From 4-7h:

The general protocol A was followed using $Al(OTf)_3$ (5.5 mg, $1.2*10^{-2}$ mmol) and 2,3-DHF **4-7h** (75.5 mg, $2.34*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.2 mL). The reaction was quenched and column chromatography (5% Et_2O/hexane, R_f = 0.26) afforded **4-8h** (60.2 mg, 93%) as a white solid (mp: 121-123 °C).

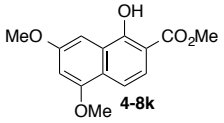
From 4-7i:

The general protocol A was followed using $Al(OTf)_3$ (5.1 mg, $1.1*10^{-2}$ mmol) and 2,3-DHF **4-7i** (77.7 mg, $2.22*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.1 mL). The reaction was quenched and column chromatography afforded **4-8h** (53.8 mg, 88%) as a white solid.

From 4-7j:

The general protocol A was followed using $Al(OTf)_3$ (4.5 mg, $9.5*10^{-3}$ mmol) and 2,3-DHF **4-7j** (73.0 mg, $1.90*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.0 mL). The reaction was quenched and column chromatography afforded **4-8h** (43.9 mg, 80%) as a white solid.

Ethyl 1-hydroxy-5,7-dimethoxy-2-naphthoate (4-8h). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.97 (s, 1 H), 7.62 - 7.67 (m, 1 H), 7.57 - 7.61 (m, 1 H), 7.24 - 7.28 (m, 1 H), 6.62 (d, J = 2.4 Hz, 1 H), 4.45 (q, J = 7.2 Hz, 2 H), 3.96 (s, 3 H), 3.95 (s, 3 H), 1.45 (t, J = 7.2 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.3, 159.3, 158.3, 156.2, 126.2, 125.0, 121.3, 112.5, 106.9, 100.7, 93.7, 61.4, 55.7, 55.5, 14.2. **IR**: 3112.3 (w), 2990.8 (w), 2939.3 (w), 2832.8 (w), 1660.7 (m), 1606.9 (s), 1442.2 (m), 1247.7 (s), 1200.5 (m), 1175.1 (s), 1026.6 (m), 799.2 (m). **HRMS** (ESI) *m/z*: [M-H$^+$] calcd. for $C_{15}H_{17}O_5$, 277.1071; found, 277.1068.



4-8k

From 4-7k:

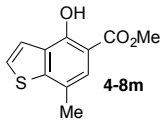
The general protocol A was followed using $Al(OTf)_3$ (6.3 mg, 1.3*10^{-2} mmol) and 2,3-DHF **4-7k** (73.4 mg, 2.19*10^{-1} mmol) in anhydrous $PhCH_3$ (1.2 mL) at **70 °C**. The reaction was quenched and column chromatography (5% Et_2O/hexane, R_f = 0.29) afforded **4-8k** (54.4 mg, 95%) as a white solid (mp: 157-159 °C).

From 4-7l:

The general protocol A was followed using $Al(OTf)_3$ (5.5 mg, 1.2*10^{-2} mmol) and 2,3-DHF **4-7l** (74.6 mg, 2.15*10^{-1} mmol) in anhydrous $PhCH_3$ (1.1 mL). The reaction was quenched and column chromatography afforded **4-8k** (28.8 mg, 51%) as a white solid.

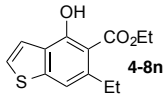
Methyl 1-hydroxy-5,7-dimethoxy-2-naphthoate (4-8k). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.87 (s, 1 H), 7.58 - 7.65 (m, 2 H), 7.26 (d, J = 2.7 Hz, 1 H), 6.62 (d, J = 2.7 Hz, 1 H), 3.99

(s, 3 H), 3.96 (s, 3 H), 3.95 (s, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.6, 159.3, 158.3, 156.3, 126.2, 125.1, 121.2, 112.7, 106.7, 100.8, 93.7, 55.7, 55.5, 52.3. **IR**: 3012.0 (w), 2965.3 (w), 2923.0 (w), 1663.3 (m), 1606.0 (m), 1443.1 (m), 1407.7 (m), 1334.5 (m), 1248.0 (s), 1198.4 (s), 1144.9 (s), 800.8 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{14}H_{14}O_5$, 262.0841; found, 262.0845.



4-8m

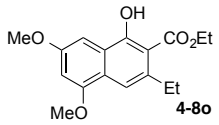
Methyl 4-hydroxy-7-methyl-3a,7a-dihydrobenzo[*b*]thiophene-5-carboxylate (4-8m). The general protocol B was followed using $Al(OTf)_3$ (29.5 mg, $6.22*10^{-2}$ mmol) and 2,3-DHF **4-7m** (75.0 mg, $2.95*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.7 mL). The reaction was quenched and column chromatography (5% Et_2O/hexane, R_f = 0.40) afforded **4-8m** (52.4 mg, 80%) as a white solid (mp: 90-92 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.39 (s, 1 H), 7.64 (d, *J* = 5.5 Hz, 1 H), 7.50 (s, 1 H), 7.37 (d, *J* = 5.5 Hz, 1 H), 3.96 (s, 3 H), 2.46 (s, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.3, 156.6, 147.5, 129.3, 125.0, 123.7, 122.4, 122.2, 106.5, 52.1, 19.4. **IR**: 3103.7 (w), 3080.1 (w), 2951.8 (m), 2917.3 (m), 2856.0 (w), 1661.1 (s), 1616.3 (m), 1431.7 (s), 1361.2 (s), 1254.3 (s), 1151.7 (s), 763.5 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{11}H_{10}O_3S$, 222.0351; found, 222.0352.



4-8n

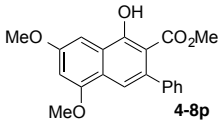
Ethyl 6-ethyl-4-hydroxy-3a,7a-dihydrobenzo[*b*]thiophene-5-carboxylate (4-8n). The general protocol B was followed using $Al(OTf)_3$ (22.8 mg, $4.81*10^{-2}$ mmol) and 2,3-DHF **4-**

7n (75.0 mg, 2.53*10^{-1} mmol) in anhydrous $PhCH_3$ (2.0 mL). The reaction was quenched and column chromatography (5% Et_2O/hexane, R_f = 0.38) afforded **4-8n** (43.4 mg, 69%) as a white solid (mp: 66-68 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 12.33 (s, 1 H), 7.58 (d, *J* = 5.5, 1 H), 7.27 (d, *J* = 5.5, 1 H), 7.22 (s, 1 H), 4.47 (q, *J* = 7.2 Hz, 2 H), 3.05 (q, *J* = 7.3 Hz, 2 H), 1.46 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.3 Hz, 3 H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.3, 159.6, 145.9, 142.3, 128.5, 124.2, 121.7, 114.7, 106.1, 61.6, 30.0, 16.4, 14.0. **IR**: 3132.3 (w), 3095.9 (w), 2987.4 (m), 2956.5 (m), 2870.3 (m), 1641.5 (s), 1607.1 (s), 1533.7 (s), 1372.9 (s), 1323.3 (s), 1249.3 (s), 1164.2 (s), 1022.3 (s), 773.9 (s). **HRMS** (EI) *m/z*: [M$^+$] calcd. for $C_{13}H_{14}O_3S$, 250.0664; found, 250.0665.



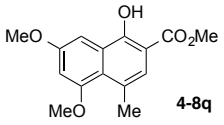
4-8o

Ethyl 3-ethyl-1-hydroxy-5,7-dimethoxy-2-naphthoate (4-8o). The general protocol B was followed using $Al(OTf)_3$ (21.5 mg, 4.53*10^{-2} mmol) and 2,3-DHF **4-7o** (77.6 mg, 2.21*10^{-1} mmol) in anhydrous $PhCH_3$ (1.5 mL). The reaction was quenched and column chromatography (5% Et_2O/hexane, R_f = 0.23) afforded **4-8o** (59.2 mg, 88%) as a white solid (mp: 105-106 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.62 (s, 1 H), 7.45 (s, 1 H), 7.23 (d, *J* = 2.1 Hz, 1 H), 6.59 (d, *J* = 2.1 Hz, 1 H), 4.48 (q, *J* = 7.3 Hz, 2 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 3.06 (q, *J* = 7.3 Hz, 1 H), 1.46 (t, *J* = 7.3 Hz, 3 H), 1.26 (t, *J* = 7.3 Hz, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.6, 160.8, 157.6, 155.6, 138.3, 124.9, 124.0, 113.5, 106.8, 100.8, 93.8, 61.6, 55.6, 55.4, 30.1, 16.5, 14.0. **IR**: 3108.1 (w), 2964.7 (m), 2937.1 (w), 2832.1 (w), 1640.1 (s), 1578.9 (s), 1416.5 (s), 1326.1 (s), 1243.9 (s), 1199.9 (s), 1148.4 (s), 1030.0 (s), 823.5 (s). **HRMS** (EI) *m/z*: [M-H$^+$] calcd. for $C_{17}H_{21}O_5$, 305.1384; found, 305.1379.



4-8p

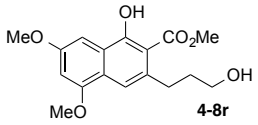
Methyl 1-hydroxy-5,7-dimethoxy-3-phenyl-2-naphthoate (4-8p). The general protocol B was followed using $Al(OTf)_3$ (24.9 mg, $5.25*10^{-2}$ mmol) and 2,3-DHF **4-7p** (85.0 mg, $2.29*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.5 mL). The reaction was quenched and column chromatography (5% Et_2O/hexane, R_f = 0.20) afforded **4-8p** (67.1 mg, 79%) as a light yellow solid (mp: 144-145 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.95 (s, 1 H), 7.54 (d, J = 0.6 Hz, 1 H), 7.35 - 7.40 (m, 2 H), 7.30 - 7.34 (m, 3 H), 7.29 (d, J = 1.8 Hz, 1 H), 6.63 (d, J = 2.4 Hz, 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H), 3.53 (s, 3 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.4, 159.5, 158.4, 156.3, 143.7, 136.2, 128.4 (2C), 127.4 (2C), 126.3, 125.4, 123.4, 115.6, 106.8, 101.1, 93.8, 55.6, 55.5, 51.7. **IR**: 3030.2 (w), 2955.2 (w), 1653.1 (s), 1595.0 (s), 1437.6 (s), 1327.9 (s), 1244.5 (s), 1202.1 (s), 1050.3 (m), 1011.2 (m), 768.9 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{20}H_{18}O_5$, 338.1154; found, 338.1141.



4-8q

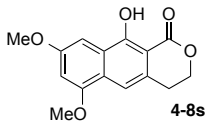
Methyl 1-hydroxy-5,7-dimethoxy-4-methyl-2-naphthoate (4-8q). The general protocol B was followed using $Al(OTf)_3$ (24.2 mg, $5.10*10^{-2}$ mmol) and 2,3-DHF **4-7q** (78.2 mg, $2.54*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.5 mL). The reaction was quenched and column chromatography (5% Et_2O/hexane, R_f = 0.23) afforded **4-8q** (60.1 mg, 86%) as a white solid (mp: 139-140 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.64 (s, 1 H), 7.29 - 7.35 (m, 2 H), 6.61 (d, J = 2.4 Hz, 1 H), 3.98 (s, 3 H), 3.94 (s, 3 H), 3.88 (s, 3 H), 2.72 (s, 3 H). **^{13}C NMR** (125

MHz, $CDCl_3$): δ 171.4, 158.9, 157.8, 157.5, 127.6, 125.5, 124.4, 122.9, 105.8, 101.6, 94.5, 55.4, 55.4, 52.2, 24.4. **IR**: 3113.6 (w), 3002.5 (w), 2954.0 (m), 2859.8 (w), 1662.6 (s), 1609.2 (s), 1509.5 (m), 1439.0 (s), 1383.9 (m), 1245.3 (s), 1204.1 (s), 1171.1 (s), 1150.0 (s), 1070.6 (m), 1017.5 (m), 797.5 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{15}H_{16}O_5$, 276.0998; found, 276.0997.



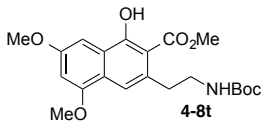
4-8r

Methyl 1-hydroxy-3-(3-hydroxypropyl)-5,7-dimethoxy-2-naphthoate (4-8r). The general protocol A was followed using $Al(OTf)_3$ (7.9 mg, $1.7*10^{-2}$ mmol) and 2,3-DHF **4-7r** (55.0 mg, $1.72*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.0 mL). The reaction was quenched and column chromatography (50% Et_2O/hexane, R_f = 0.12) afforded **4-8r** (46.5 mg, 85%) as a light yellow solid (mp: 108-109 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.49 (s, 1 H), 7.45 (s, 1 H), 7.23 (s, 1 H), 6.58 - 6.62 (m, 1 H), 4.01 (s, 3 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 3.70 (t, J = 6.1 Hz, 2 H), 3.05 - 3.14 (m, 2 H), 1.83 - 1.93 (m, 2 H), 1.27 - 1.41 (m, 1 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.9, 161.0, 157.9, 155.7, 135.5, 125.1, 123.9, 114.5, 106.7, 101.0, 93.9, 62.8, 55.7, 55.5, 52.2, 34.9, 33.4. **IR**: 3010.5 (w), 2957.3 (w), 1652.4 (m), 1600.9 (s), 1437.1 (m), 1332.7 (m), 1250.4 (s), 1205.1 (s), 1047.6 (m), 806.9 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{17}H_{20}O_6$, 320.1260; found, 320.1266.



4-8s

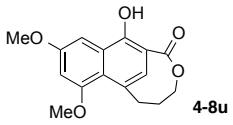
10-Hydroxy-6,8-dimethoxy-3,4-dihydro-1*H*-benzo[*g*]isochromen-1-one (4-8s). The general protocol A was followed using $Al(OTf)_3$ (6.6 mg, $1.4*10^{-2}$ mmol) and 2,3-DHF **4-7s** (73.5 mg, $2.40*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.2 mL). The reaction was quenched and column chromatography (20% Et_2O/hexane, R_f = 0.20) afforded **4-8s** (59.3 mg, 90%) as a yellow solid (mp: 149-150 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.13 (s, 1 H), 7.41 (d, *J* = 0.9 Hz, 1 H), 7.22 (d, *J* = 2.1 Hz, 1 H), 6.64 (d, *J* = 2.1 Hz, 1 H), 4.54 - 4.65 (m, 2 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 3.12 - 3.17 (m, 2 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.9, 160.4, 158.1, 155.9, 129.8, 125.2, 124.9, 110.1, 103.3, 101.6, 93.9, 68.7, 55.7, 55.6, 28.0. **IR**: 2949.1 (m), 2836.6 (w), 1659.0 (s), 1608.3 (s), 1401.1 (s), 1201.7 (s), 1161.4 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{15}H_{14}O_5$, 274.0841; found, 274.0839.



4-8t

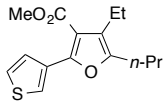
Methyl 3-(2-((*tert*-butoxycarbonyl)amino)ethyl)-1-hydroxy-5,7-dimethoxy-2-naphthoate (4-8t). The general protocol A was followed using $Al(OTf)_3$ (5.0 mg, $1.1*10^{-2}$ mmol) and 2,3-DHF **4-7t** (74.0 mg, $1.83*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.2 mL). The reaction was quenched and column chromatography (20% Et_2O/hexane, R_f = 0.11) afforded **4-8t** (12.8 mg, 17%) as a white solid (mp: 132-133 °C) along with unreacted DHF **4-7t** (26.0 mg, 35% recovered). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.55 (s, 1 H), 7.42 (s, 1 H), 7.23 (d, *J* = 2.1 Hz, 1 H), 6.60 (d, *J* = 2.1 Hz, 1 H), 4.49 - 4.61 (bs, 1 H), 4.02 (s, 3 H), 3.94 (s, 3 H), 3.93 (s, 3 H), 3.39 (t, *J* = 6.9 Hz, 2 H), 3.19 (t, *J* = 6.9 Hz, 2 H), 1.38 - 1.47 (s, 9 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.7, 161.2, 158.1, 155.9, 155.7, 132.1, 125.4, 123.8, 115.5, 106.6, 101.1, 93.9, 55.6, 55.5, 52.4, 41.9, 37.4, 28.4. **IR**: 3402.6 (w), 2948.5 (m), 1700.6 (m), 1648.1 (m),

1600.1 (m), 1492.2 (m), 1436.8 (m), 1332.5 (m), 1246.6 (s), 1205.0 (s), 1165.9 (s), 1051.1 (m), 807.9 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{21}H_{27}NO_7$, 405.1788; found, 405.1789.



4-8u

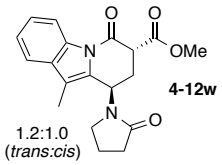
1-Hydroxy-9,11-dimethoxy-6,7-dihydro-3*H*,5*H*-2,8-(metheno)benzo[*e*]oxecin-3-one (4-8u). The general protocol B was followed using $Al(OTf)_3$ (25.5 mg, $5.38*10^{-2}$ mmol) and a mixture of 2,3-DHF **4-7u** and **4-7u'** (84.0 mg, $2.62*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.5 mL). The reaction was quenched and column chromatography (5% Et_2O/hexane, R_f = 0.20) afforded **4-8u** (34.3 mg, 47%) as a white solid (mp: 139-140 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.75 (s, 1 H), 7.44 (d, *J* = 2.7 Hz, 1 H), 7.34 (s, 1 H), 6.87 (d, *J* = 2.7 Hz, 1 H), 4.26 (t, *J* = 7.2 Hz, 2 H), 3.98 (s, 3 H), 3.92 (s, 3 H), 3.15 (dd, *J* = 6.9, 6.0 Hz, 2 H), 2.17 - 2.26 (m, 2 H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.4, 160.2, 158.4, 157.9, 128.3, 127.8, 127.0, 120.6, 111.6, 105.4, 98.3, 73.1, 55.5, 52.2, 31.5, 29.5. **IR**: 3003.5 (w), 2949.1 (m), 2852.0 (w), 1661.3 (s), 1610.5 (s), 1409.7 (s), 1251.2 (s), 1162.4 (s), 1060.3 (s), 800.5 (s). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{16}H_{16}O_5$, 288.0998; found, 288.0994.



4-4v

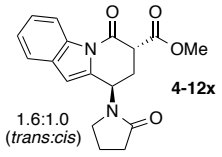
Methyl 4-ethyl-5-propyl-2-(thiophen-3-yl)furan-3-carboxylate (4-4v). The general protocol B was followed using $Al(OTf)_3$ (33.5 mg, $7.06*10^{-2}$ mmol) and 2,3-DFH **4-7v** (106 mg, $3.41*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.2 mL). The reaction was quenched and column chromatography (5% Et_2O/hexane, R_f = 0.33) afforded **4-4v** (84.8 mg, 89%) as a light yellow

oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.02 - 8.11 (m, 1 H), 7.56 - 7.63 (m, 1 H), 7.30 (dd, *J* = 5.1, 3.1 Hz, 1 H), 3.85 (s, 3 H), 2.51 - 2.65 (m, 4 H), 1.59 - 1.75 (m, 2 H), 1.12 (t, *J* = 7.5 Hz, 3 H), 0.96 (t, *J* = 7.3 Hz, 3 H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.1, 151.9, 150.5, 131.4, 127.3, 124.9, 124.7, 122.4, 112.6, 51.2, 27.6, 21.9, 17.7, 15.6, 13.7. **IR**: 2962.7 (m), 2872.0 (w), 1737.9 (s), 1712.8 (s), 1437.0 (m), 1371.4 (m), 1238.3 (s), 1089.8 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{15}H_{18}O_3S$, 278.0977; found, 278.0983.



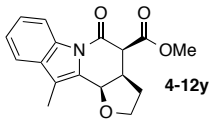
Methyl 10-methyl-6-oxo-9-(2-oxopyrrolidin-1-yl)-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (4-12w). The general protocol A was followed using 4 Å molecular sieves (1-2 mm beads, 0.6-0.8 g), $Al(OTf)_3$ (18.2 mg, $3.84*10^{-2}$ mmol) and a mixture of 2,3-DHF **4-7w** and side product **4-7w'** (65.0 mg, $1.91*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.2 mL) at **50 °C**. The reaction was quenched and column chromatography (50% EtOAc/hexane, R_f = 0.07) afforded **4-12w** (49.9 mg, 77%) as a yellow oil. *Diastereomeric mixture*: 1.2:1 (*trans:cis* ratio) **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.41 - 8.46 (m, 1.85, major + minor), 7.49 (dd, *J* = 7.5, 0.6 Hz, 1.00, major), 7.45 - 7.48 (m, 0.85, minor), 7.30 - 7.40 (m, 3.70, major + minor), 5.71 (td, *J* = 5.4, 4.4 Hz, 0.86, minor), 5.67 (t, *J* = 5.0 Hz, 1.00, major), 3.89 (t, *J* = 7.8 Hz, 1.00, major), 3.82 - 3.86 (m, 3.40, minor), 3.82 (s, 3.00, major), 3.26 - 3.34 (m, 0.85, minor), 3.12 - 3.25 (m, 1.85, major + minor), 3.08 (ddd, *J* = 9.5, 8.2, 6.1 Hz, 1.00, major), 2.71 - 2.81 (m, 0.85, minor), 2.57 - 2.63 (m, 2.00, major), 2.43 - 2.53 (m, 3.70, major + minor), 2.30 (dt, *J* = 13.0, 5.1 Hz, 0.85, minor), 2.16 (d, *J* = 0.6 Hz, 3.00, major), 2.13 (d, *J* = 1.2 Hz, 2.55, minor), 1.90 - 2.09 (m, 3.70, major + minor). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.2, 175.1,

169.0, 168.9, 164.3, 164.1, 134.7, 134.6, 130.9, 130.5, 128.9, 128.7, 125.8, 125.6, 124.5, 124.4, 118.6, 118.3, 117.0, 116.7, 116.5, 116.0, 53.0, 52.8, 48.9, 48.2, 45.5, 44.5, 43.2, 42.7, 30.9, 30.9, 29.7, 28.4, 18.3, 17.9, 8.3, 8.1. **IR**: 3059.5 (w), 2952.4 (m), 2910.2 (m), 1741.0 (s), 1683.9 (s), 1457.3 (m), 1385.0 (m), 1267.3 (m), 752.7 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{19}H_{20}N_2O_4$, 340.1423; found, 340.1428.

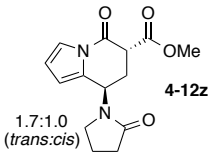


Methyl 6-oxo-9-(2-oxopyrrolidin-1-yl)-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (4-12x). The general protocol A was followed using 4 Å molecular sieves (1-2 mm beads, 0.6-0.8 g), $Al(OTf)_3$ (6.0 mg, $1.3*10^{-2}$ mmol) and 2,3-DHF **4-7x** (51.7 mg, $1.58*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.0 mL). The reaction was quenched and column chromatography (60% EtOAc/hexane, R_f = 0.10) afforded **4-12x** (31.2 mg, 60%) as a colorless oil. *Diastereomeric mixture*: 1.6:1 (*trans:cis* ratio). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.43 - 8.47 (m, 0.61, minor), 8.37 - 8.42 (m, 1.00, major), 7.45 - 7.50 (m, 1.61, major + minor), 7.26 - 7.36 (m, 3.20, major + minor), 6.32 - 6.36 (m, 0.61, minor), 6.26 - 6.30 (m, 1.00, major), 5.66 - 5.73 (m, 1.61, major + minor), 3.92 - 3.98 (m, 1.61, major + minor), 3.87 (s, 3.00, major), 3.80 (s, 1.83, minor), 3.47 (m, 1.00, major), 3.25 - 3.39 (m, 2.22), 2.64 (q, *J* = 13.0 Hz, 1.00, major), 2.48 - 2.60 (m, 4.44, major + minor), 2.27 (dt, *J* = 12.4, 4.6 Hz, 1.00, major), 2.06 - 2.17 (m, 3.22, major + minor). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.5, 175.3, 168.7, 168.6, 164.4, 163.7, 135.3, 135.2, 134.8, 134.7, 129.2, 129.2, 125.1, 125.1, 124.6, 124.6, 120.4, 120.3, 116.5, 116.4, 106.9, 106.1, 53.2, 52.9, 49.8, 49.1, 45.3, 43.8, 43.4, 42.5, 31.0, 31.0, 28.9, 28.8, 18.3, 18.3. **IR**: 3050.7 (w), 2965.4 (w), 1742.6 (m), 1683.2 (s), 1596.1

(m), 1454.3 (m), 1351.1 (m), 1283.3 (m), 1164.7 (m), 755.6 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{18}H_{18}N_2O_4$, 326.1267; found, 326.1264.



Methyl 11-methyl-5-oxo-2,3,3a,4,5,11b-hexahydrofuro[2',3':3,4]pyrido[1,2-*a*]indole-4-carboxylate (4-12y). The general protocol A was followed using $Al(OTf)_3$ (12.0 mg, $2.53*10^{-2}$ mmol) and 2,3-DHF **4-7y** (100 mg, $3.34*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.7 mL). The reaction was quenched and column chromatography (20% EtOAc/hexane, R_f = 0.30) afforded **4-12y** (85.4 mg, 85%) as a colorless oil. Spectral data matches with reported values.[14b]



Methyl 5-oxo-8-(2-oxopyrrolidin-1-yl)-5,6,7,8-tetrahydroindolizine-6-carboxylate (4-12z). The general protocol A was followed using 4 Å molecular sieves (1-2 mm beads, 0.6-0.8 g), $Al(OTf)_3$ (12.5 mg, $2.64*10^{-2}$ mmol) and 2,3-DHF **4-7z** (70.3 mg, $2.54*10^{-1}$ mmol) in anhydrous $PhCH_3$ (1.3 mL). The reaction was quenched and column chromatography (70% EtOAc/hexane, R_f = 0.12) afforded **4-12z** (37.7 mg, 54%) as a colorless oil. *Diastereomeric mixture*: 1.7:1 (*trans*:*cis* ratio) **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 3.4, 0.9 Hz, 0.60, minor), 7.35 (dd, *J* = 1.8, 1.2 Hz, 1.00, major), 6.24 - 6.31 (m, 1.60, major + minor), 6.00 (dt, *J* = 3.1, 1.5 Hz, 0.60, minor), 5.93 (dt, *J* = 3.1, 1.6 Hz, 1.00, major), 5.45 - 5.60 (m, 1.60, major + minor), 3.79 - 3.88 (m, 4.60, major + minor), 3.78 (s, 1.8, minor), 3.39 (ddd, *J* = 9.3,

7.6, 5.6 Hz, 1.00, major), 3.22 - 3.30 (m, 1.60, major + minor), 3.16 - 3.22 (m, 0.60, minor), 2.39 - 2.51 (m, 5.40, major + minor), 2.22 (dt, *J* = 12.5, 4.7 Hz, 1.0, major), 1.99 - 2.12 (m, 3.20, major + minor). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.5, 175.3, 168.5, 168.3, 163.5, 163.0, 129.9, 129.7, 117.8, 117.6, 113.5, 113.5, 111.1, 111.2, 53.2, 52.8, 49.0, 48.1, 45.0, 43.7, 43.4, 42.5, 31.1, 31.0, 29.6, 29.4, 18.3, 18.2. **IR**: 2956.5 (m), 1715.5 (s), 1677.0 (s), 1406.9 (s), 1271.8 (s), 1138.1 (m), 735.7 (m). **HRMS** (EI) *m/z*: [M^+] calcd. for $C_{14}H_{16}N_2O_4$, 276.1110; found, 276.1103.

4.5 References

1. a) Mortensen, D. S.; Rodriguez, A. L.; Carlson, K. E.; Sun, J.; Katzenellen-bogen, B.S.; Katzenelienbogen, J.A. *J. Med. Chem.* **2001**, *44*, 3838-3848; b) Coll, J.; Tandron, Y. A. *Phytochem. Rev.* **2007**, *7*, 25-49; c) Fraga, B. M. *Nat. Prod. Rep.* **1992**, *9*, 217-241; d) Merritt, A. T.; Ley, S. V. *Nat. Prod. Rep.* **1992**, *9*, 243-287.
2. a) Arai, S.; Nakayama, K.; Suzuki, Y.; Hatano, K.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 9739-9742; b) Pohmakotr, M.; Issaree, A.; Sampaongoen, L.; Tuchinda, P.; Reutrakul, V. *Tetrahedron Lett.* **2003**, *44*, 7937-7940.
3. Maiti, S.; Perumal, P. T.; Menendez, J. C. *Tetrahedron* **2010**, *66*, 9512-9518.
4. a) Kumar, A.; Srivastava, S.; Gupta, G.; Chaturvedi, V.; Sinha, S.; Srivastava, R. *ACS Comb. Sci.* **2011**, *13*, 65-71; b) Chagarovsky, A. O.; Budynina, E. M.; Ivanova, O. A.; Villemson, E. V.; Rybakov, V. B.; Trushkov, I. V.; Melnikov, M. Y. *Org. Lett.* **2014**, *16*, 2830-2833.

5. Chauhan, S.; Mane, G. P.; Anand, C.; Dhawale, D. S.; Reddy, B. V. S.; Zaidi, S. M. J.; Al-Deyab, S. S.; Balasubramanian, V. V.; Mori, T.; Vinu, A. *Synlett* **2012**, *23*, 2237.

6. a) Morel, A.; Trzeciak, A. M.; Pernak, J.; *Molecules*, **2014**, *19*, 8402-8413; b) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T. *Organometallics* **1993**, *12*, 4188-4196.

7. Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1987**, *28*, 175-178.

8. F. Garzino, A. Meou, P. Brun, *Tetrahedron Lett.* **2002**, *43*, 5049-5051

9. Yang, F. Z.; Trost, M. K.; Fristad, W. E. *Tetrahedron Lett.* **1987**, *28*, 1493.

10. Xia, L.; Lee, Y. R.; Kim, S. H.; Lyoo, W. S. *Bull. Korean Chem. Soc.* **2011**, *32*, 1554.

11. Sugiura, M.; Hagio, H.; Hirabayashi, R,; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510-12517.

12. a) Kim, J.-B.; Cho, I. *J. Polym. Sci., Part A: Polym. Chem.* **1989**, *27*, 3733-3744; b) Nuyken, O;. Braun, H. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **2001**, *42*, 779-780; c) Nuyken, O.; Braun, H. *Des. Monomers Polym.* **2001**, *4*, 19-26.

13. For applications of (hetero)aromatics see Chapter 1.

14. a) Phun, L. H.; Patil, D. V.; Cavitt, M. A. *Org. Lett*. **2011**, *13*, 1952; b) Patil, D. V.; Cavitt, M. A.; Grzybowski, P.; France, S. *Chem. Comm.* **2011**, *47*, 10278; c) Phun, L. H.; Aponte-Guzman, J.; France, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3198; d) Martin, M. C.; Patil, D. V.; France, S. *J. Org. Chem.* **2014**, *79*, 3030; h) Cavitt, M. C.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804.

15. a) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413-445; b) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2007**, *11*, 925-957; c) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2012**, *16*, 1277-1312.

16. While 2,5-dimethoxytetrahydrofuran (DMTHF) has been employed in benzannulation reactions, DHF acetals have not been utilized in that same capacity (to the best of our knowledge). For a representative example of benzannulation with DMTHF, see: Rafiq, S. M.; Sivasakthikumaran, R.; Mohanakrishnan, A. K. *Org. Lett.* **2014**, *16*, 2720.

17. Davies, H. M. L.; Ahmed, G.; Calvo, R. L.; Churchill, M. R.; Churchill, D. G. *J. Org. Chem.* **1998**, *63*, 2641-2645.

18. a) Guzi, T. J. et al (**2004**). *U.S. Patent No. 2004010662 4A1*. Washington, DC: U.S. Patent and Trademark Office; b) Sridhar, Y.; Srihari, P. *Eur. J. Org. Chem.* **2013**, *3*, 578-587.

19. Pasceri, R.; Bartrum, H. E.; Hayes, C. J.; Moody, C. J. *Chem. Comm.* **2012**, *48*, 12077-12079.

20. Baburajan, P.; Elango, K. P. *Tetrahedron Letters* **2014**, *55*, 3525-3528.

21. Lamotte, G.; Demerseman, P.; Royer, R. *Synthesis* **1984**, *12*, 1068-1070.

22. Kumar, S.; Namkung, W.; Verkman, A. S.; Sharma, P. K. *Bioorg. Med. Chem.* **2012**, *20*, 4237-4244.

23. Marcus, A. P.; Lee, A. S.; Davis, R. L.; Tantillo, D. J.; Sarpong, R. *Angew. Chem. Int. Ed.* **2008**, *47*, 6379-6383.

CHAPTER 5

A TANDEM, BICATALYTIC CONTINUOUS FLOW CYCLOPROPANATION-HOMO-NAZAROV-TYPE CYLIZATION

The work about to be presented is adapted from a previous publication. For a better understanding on the topic, access the corresponding reference.[22] The experimental section includes all the data for cyclopropanes **5-5** and their corresponding cycloisomerized products **5-6** obtained by the three first authors. My contribution on this project includes: batch reaction optimizations for **5-5a** (cyclopropanation), **5-6a** (cyclization), **5-6a** (tandem protocol), and **5-6d** (cyclization); as well as the purification of the continuous flow reactions. Shenje, R. was responsible for the batch optimization of **5-5b** (cyclopropanation), **5-5c** (cyclopropanation), **5-6c** (cyclization), and **5-6c** (tandem protocol); as well as the purification of the continuous flow reactions. Huang, Y.; Woodham, W. H.; and Saunders, S. R were responsible of building and operating the continuous flow reactor.

5.1 Introduction

Historically, batch processing has been the major strategy in the synthesis of complex molecules, especially molecules of pharmaceutical interest. In general, this approach has been fraught with high cost, excessive time for scale-up, and waste issues.[1] In order to address these issues, continuous flow technology has been identified as an alternative production vehicle since it has both environmental and economic advantages. For instance, the transfer from batch to continuous flow maximizes performance in terms of product yield and selectivity while minimizing solvent and catalyst needs, thereby lowering production

costs.[2-4] When compared with the traditional batch technology, continuous flow offers a reduced manual handling, higher control of the reaction variables, increased safety, the possibility of in-line purification, between many other advantages highlighted in several reports.[1b,5] However, the large majority of reaction processes are still run in batch with a slow gradual change to continuous flow technology.

Multistep continuous flow processes can provide a potential tool to the pharmaceutical companies for accessing complex molecules.[1b] To this end, many synthetic reports have made use of this technology, proving particular advantages of each protocol.[6-7] Recently, Ley and co-workers reported a seven-step continuous flow synthesis of oxamaritidine, requiring only one solvent change. No purification was employed in order to obtain the complex natural product in excellent yield (>40%) and in over 90% purity.[8] In contrast, the combination of five separate flow steps reported by Martinelli required multiple solvent changes and in-flow purification techniques to obtain (+)-dumetorine in ~30% yield. However, this yield was much higher than the ~1% overall yield utilizing batch processes.[9]

Despite the many advantages obtained by utilizing multistep flow technologies, there are still some challenges that need to be overcome depending on the type of reaction(s). Some of these include, but are not limited to, solvent compatibility, in-flow purification, and concentration management at each step of the synthetic procedure.[10] Nevertheless, the integration of chemical engineering and chemical reaction design has helped with some of these issues. This can be observed in the multistep one-flow syntheses (no solvent change) of grossamide[11] and tamoxifen[12] reported by Ley. Similarly, Snead and Jamison disclosed a 3 min continuous flow synthesis and purification of ibuprofen with a throughput of ~8 g per hour.[13]

Previously, our lab reported the batch synthesis of hydropyrido[1,2-*a*]indoles **5-6** from *N*-indolyl 1,1-cyclopropane β-amidoesters **5-5**[14] via $In(OTf)_3$-catalyzed, homo-Nazarov-type[15-17] cyclizations (21 examples). The cyclopropanes required for this transformation were prepared in three steps from the corresponding 1*H*-indoles **5-1** via acylation, diazo transfer, then Rh(II)-catalyzed cyclopropanation (Figure 5-1a), with purifications performed for each step. We later utilized this general sequence in the six-step synthesis of the indole alkaloid deethyleburnamonine (Figure 5-1b). Inspired by these reports, we decided to take advantage of continuous flow technology to conduct the multistep synthesis (four steps) of the hydropyrido[1,2-*a*]indole framework, which is present in many naturally occurring indole alkaloids and pharmaceutically relevant compound.[18-21] The use of continuous flow would be beneficial in dealing with the generation and use of reactive Rh-carbenoid species in a controlled and reproducible fashion while alleviating any large-scale safety concerns. Herein, we report the development of a two-step flow synthesis of hydropyrido[1,2-*a*]indoles: the tandem, bicatalytic cyclopropanation-homo-Nazarov-type ring-opening cyclization.[22]

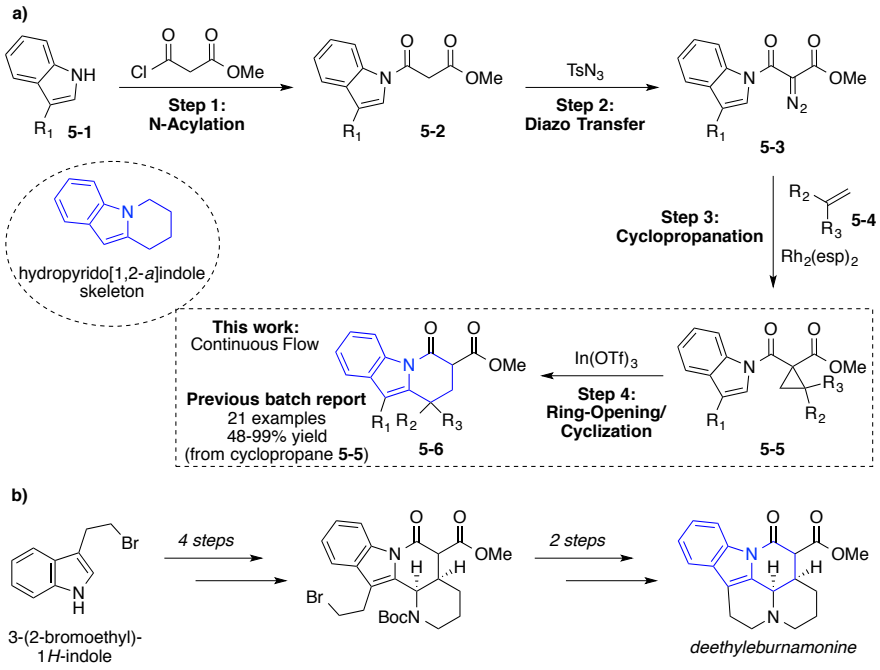


Figure 5-1. (a) Development of a four-step continuous flow synthesis of hydropyrido[1,2-*a*]indoles and (b) application toward deethyleburnamonine.

5.2 Reactor Design

5.2.1 Single-step reactor

A simple plug flow reactor was developed to conduct the individual ring-opening cyclizations and cyclopropanations (Figure 5-2a). The reactor featured a straightforward design with three principal components: (i) reagent/catalyst addition module consisting of reagent and catalyst reservoirs and two Eldex series 2000 ReciPro reciprocating pumps; (ii) a reactor module comprised of a 1/16" tee-joint where the solutions initially mix and proceed into the reactor coil (1/4" stainless steel tubing, Figure 5-2b) extending for a final reaction volume of 29.5 mL; and (iii) product collection module containing a reaction quenching agent. The system pressure and temperature were measured prior to entering the main body of the reactor. The reactor was heated (when necessary) with heating tape controlled by a

Eutech Instruments Digi-Sense temperature controller and the effluent temperature was measured before emptying into a collection flask for analysis. The reagent/catalyst concentrations and flow rates were chosen to directly mimic conditions and reaction times of batch reactions. Samples were taken at residence time intervals (~every 15 min) to establish equilibrium composition and yield.

a) **b)**

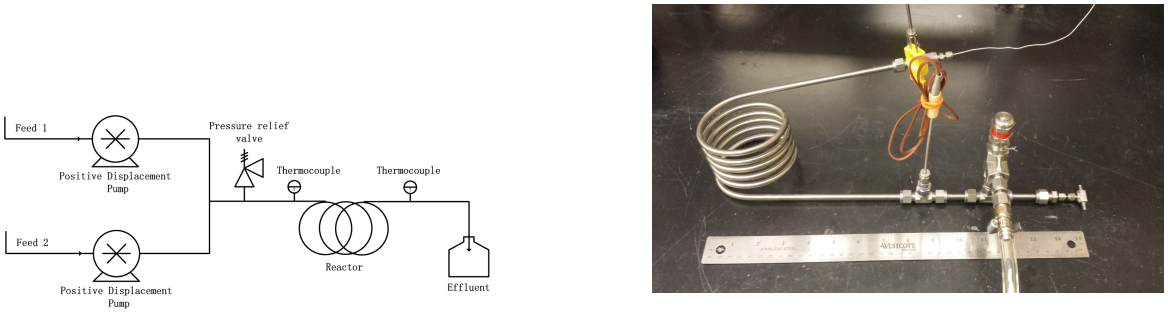


Figure 5-2. Schematic (a) and picture (b) of single plug-flow reactor apparatus.

5.2.2 Tandem reactor

To accomplish the two-step tandem reaction, the plug-flow reactor was re-designed to accommodate multiple solution inlets, proper mixing and the need for two reactor coils (Figure 5-3). The new, tandem reactor apparatus consisted of two Teledyne Isco syringe pumps that feed solutions of diazoester **3** (pump 1) and a mixture of rhodium(II) catalyst, alkene **4** and internal standard *p*-xylene (pump 2) to the 30 mL single reactor 1 as described above. The effluent of this reactor is then mixed with an $In(OTf)_3$ feed stream (pump 3) by passing through a 6 mL mixing bed packed with 2 mm borosilicate glass beads. The mixed stream is then fed into a 30 mL reactor (316 stainless steel, 0.25" OD x 0.035" wall thickness, 3.5" diameter). Heating of the system to 50 ˚C was accomplished via heating tape

wound about the reactor coil and controlled with a Digisense temperature controller. Samples were taken in 10 min intervals following the first residence time (50 min).

a) **b)**

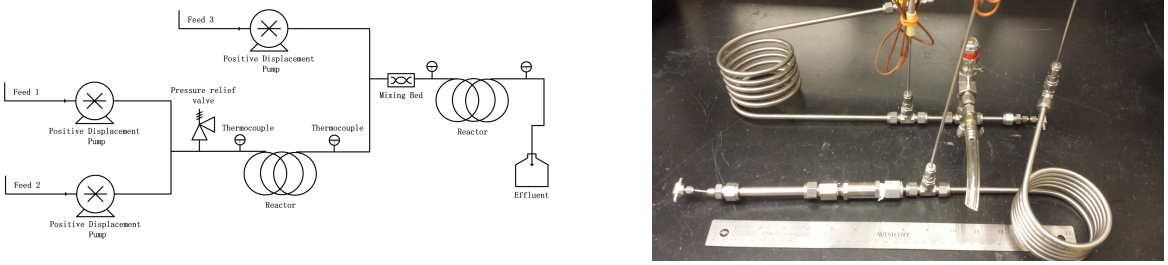


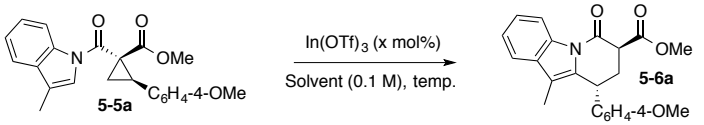
Figure 5-3. Schematic (a) and picture (b) of tandem flow reactor apparatus

5.3 Results and Discussion

5.3.1 Batch reaction optimization: Cyclopropane ring-opening cyclization

Inspired by the literature procedure reported by France and coworkers,[14] cyclopropane **5-5a** was chosen as the model system for the batch optimization studies based on its efficient conversion to hydropyrido[1,2-*a*]indole **5-6a** in >99% yield in dichloromethane in the presence of 30 mol% $In(OTf)_3$ in under 2 h. Batch reaction optimizations (Table 5-1), in terms of solvent and catalyst loading, were conducted in order to find a lower catalyst loading and a pharmaceutically- and/or industrially-suitable solvent. Given that the original reaction was complete with 15 min, we were determined to maintain that time marker in the transfer from batch to flow. **Thus, in all experiments, the reactions that were the deemed most successful, were the ones that gave complete conversion within a 15 min timeframe**. This context is central to understanding the decisions made throughout the optimization studies.

Table 5-1. Batch optimization of the ring-opening cyclization of cyclopropane 5-5a.



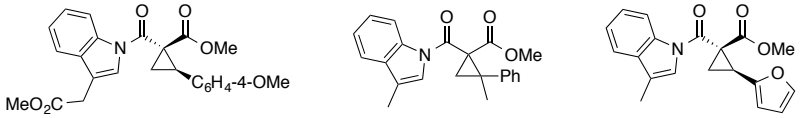
Entry	Solvent	Loading (mol%)	Temp. (°C)	Time	% Conversion[a]
1	CH_2Cl_2	30	20	< 15 min	>99
2	THF	30	20	12 hrs	>99
3	MTBE	30	20	9 hrs	>99
4	$PhCH_3$	30	20	< 15 min	>99
5	$PhCH_3$	5	20	18 hrs	~95
6	Acetone	30	20	30 min	>99
7	EtOAc	30	20	30 min	>99
8	EtOAc	10	77	30 min	>99
9	CH_3CN	30	20	< 15 min	>99
10	**CH_3CN**	**5**	**20**	**15 min**	**>99 (96)[b,c]**
11	CH_3CN	1	82	15 min	~95

a) Determined by ^{1}H NMR; b) Number in parentheses represents isolated yield after chromatography;
c) Diastereoselectivities (as determined by ^{1}H NMR) range from 1.9:1 to 2.3:1 *trans:cis dr.*

Solvents such as acetonitrile (CH_3CN), toluene ($PhCH_3$), acetone, and ethyl acetate (EtOAc) gave conversions comparable to those observed in dichloromethane (CH_2Cl_2, DCM, Table 5-1, entries 1, 4-7). Solvents containing an ether moiety, such as tetrahydrofuran (THF) or methyl *tert*-butyl ether (MTBE), were excluded from further studies due to long reaction times even when high catalyst loadings were used (Table 5-1, entries 2 and 3). Alcohols, such as methanol and isopropanol, were also excluded because no reaction was observed in these solvents within a 24 h time frame. This lack of reactivity could be attributed to the insolubility of both the $In(OTf)_3$ and cyclopropane **5-5a** as well as a potential interaction between the solvent and Lewis acid. Based upon these results, an effort was made to optimize reaction temperature and catalyst loadings in CH_3CN. At room temperature in CH_3CN, the catalyst loading could be readily reduced to 5 mol% to give full conversion within 15 min (Table 5-1, entry 10). At 1 mol% loading, full conversion was not achieved

within the 15 min window. Heating the reaction with 1 mol% catalyst at 82 ˚C failed to give full conversion within 15 min (Table 5-1, entry 11). Thus, for **5-5a**, the optimized batch conditions selected for technology transfer to continuous flow were 5 mol% $In(OTf)_3$ in CH_3CN (0.1 M) at room temperature for ~15 min.

With a working substrate in hand, we were interested in exploring the generality of the optimized conditions for other cyclopropane substrates that would ultimately be amenable to flow conditions. Cyclopropanes **5-5b** to **5-5d** were prepared and examined for compatibility (Figure 5-4). Cyclopropane **5-5b** contains different functionality on the indole moiety at the 3-position as compared to **5-5a** (methyl acetate vs methyl). **5-5c** (derived from alpha-methyl styrene) contains two geminal donor groups on the cyclopropane. The product from this substrate would contain a quaternary center. Finally, **5-5d** replaces the 4-methoxy phenyl group with a 2-furyl moiety.



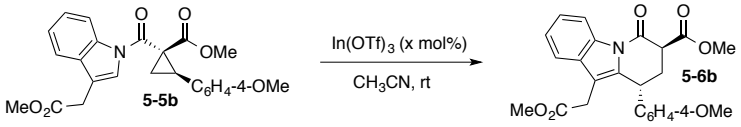
5-5b **5-5c** **5-5d**

Figure 5-4. Expanding scope of optimized reaction.

According to previous work carried out by the France lab, cyclopropane **5-5b** cyclizes in the presence of 30 mol% $In(OTf)_3$ in DCM to give **5-6b** in a 88% yield after 3 h.[14] In order to make this transformation pharmaceutically attractive and amenable to flow, we explored the use of the CH_3CN as solvent for the reaction (Table 5-2). Gratifyingly, the same optimized conditions worked for **5-5b** as did for **5-5a**. Using 5 mol% $In(OTf)_3$ in CH_3CN at room

temperature, a 90% yield of hydropyrido[1,2-*a*]indole **5-6b** was obtained (Table 5-2, entry 2).

Table 5-2. Batch optimization of the ring-opening cyclization of cyclopropane 5-5b.

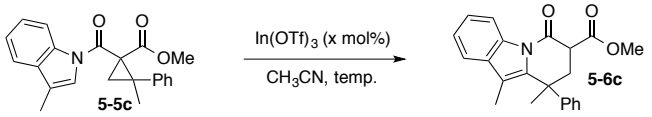


Entry	Conc. (M)	Loading (mol%)	Time (min)	% Yield[a,b]
1	0.5	1	15	71
2	**0.1**	**5**	**15**	**90**
3	0.5	5	5	85
4	1.0	15	20	>99

a) Isolated yield after chromatography; b) Diastereoselectivities (as determined by ^{1}H NMR) 1.9:1 *trans:cis dr.*

Cyclopropane **5-5c** has been previously shown to provide its product **5-6c** in 94% yield after in 2 h when using 30 mol% $In(OTf)_3$ in DCM. To make **5-5c** amenable to flow, we looked to optimize the formation of hydropyrido[1,2-a]indole **5-6c** in CH_3CN (Table 5-3). At a cyclopropane concentration of 0.2 M and a catalyst loading of 5 mol%, the reaction was slow and failed to reach >50% conversion even after 3 h in CH_3CN (Table 5-3, entry 1). Increases in both reaction concentration and catalyst loading led to increased yields, with the highest yield (63%) obtained at a concentration of **5-6c** of 1.0 M with a catalyst loading of 15 mol% after 20 min (Table 5-3, entry 6). We anticipated that an increase in temperature could help the overall reactivity. Given that, 15 mol% loading of $In(OTf)_3$ gave a good yield at room temp, we heated **5-5c** at 50 ˚C with the same loading but at a concentration of 0.1 M. We were pleased to find that product **5-6c** was obtained in quantitative yield after 15 min (Table 5-3, entry 8).

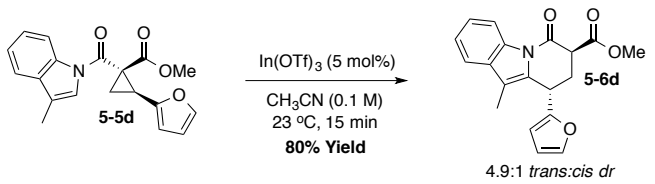
Table 5-3. Batch optimization of the ring-opening cyclization of cyclopropane 5-5c.



Entry	Conc. (M)	Loading (mol%)	Temp. (°C)	Time	% Yield[a,b]
1	0.2	5	23	> 2 hrs	not isolated
2	0.2	10	23	15 min	24
3	0.2	10	23	20 min	32
4	0.2	15	23	20 min	46
5	0.5	15	23	20 min	42
6	1.0	15	23	20 min	63
7	0.1	30	23	20 min	44
8	**0.1**	**15**	**50**	**10 min**	**> 99**

a) Isolated yield after chromatography; b) Diastereoselectivities (as determined by ^{1}H NMR) range from 1.1-1.3:1 *trans:cis dr*.

Finally, the optimization of cyclopropane **5-5d** required minimal effort as **5-5d** readily gave **5-6d** in 80% isolated yield in 10-15 min using the same conditions (5 mol% $In(OTf)_3$, CH_3CN (0.1 M)), that worked for **5-5a** and **5-5b** (Scheme 5-1). With four optimized substrates in hand, we next focused our efforts on the transfer from batch to continuous flow.



Scheme 5-1. Formation of pyrido[1,2-*a*]indole 5-6d from cyclopropane 5-5d in batch.

5.3.2 Continuous flow results: Cyclopropane ring-opening cyclization

A simple plug flow reactor was used to conduct homo-Nazarov cyclizations at batch-optimized conditions. The results of a number of continuous homo-Nazarov cyclization experiments are shown below in Figure 5-5. The first continuous flow reaction was performed with cyclopropane **5-5a** at ambient temperatures (~18 °C) and reached full conversion to **5-6a** (i.e., no starting material was detected by HPLC nor by ^{1}H NMR) after one residence time (~15 minutes). Two or three additional samples were collected from the reactor at residence times two (30 min), three (45 min), and four (60 min). Initial concentrations of cyclopropane **5-6a** and $In(OTf)_3$ upon mixing were 0.1 M and 0.005 M, respectively. The lactam **5-6a** was isolated and was found to have yields of 82%, 99%, 99% and 99% at residence times one, two, three and four, respectively.

Cyclopropanes **5-5b** and **5-5d** similarly transferred well to the continuous flow reactor at room temperature and achieved near-quantitative yield within two residence times (Figure 5-5). **5-5b** provided its product **5-6b** in 66%, 96%, 96%, and 95% yields at residence times one, two, three and four, respectively. 76%, 98%, 93% and 91% yields were obtained for hydropyrido[1,2-*a*]indole **5-6d** at the respective four residence times. For the methyl-phenyl cyclopropane **5-5c** we were pleased to find near-quantitative yields (65%, 93%, and 93% yields for residence times one, two and three, respectively).

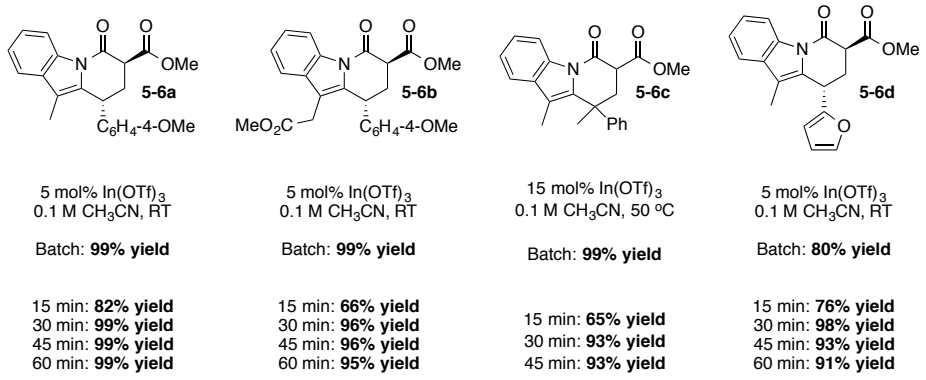


Figure 5-5. Continuous flow ring-opening cyclizations.

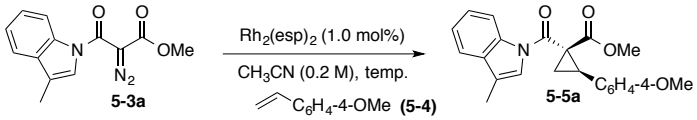
5.3.3 Batch reaction optimization: Cyclopropanation

With a working homo-Nazarov cyclization (Figure 5-1, Step 4), we next decided to work on the batch optimization of the cyclopropanation reaction (Figure 5-1, Step 3). The cyclopropanation reaction to form **5-5a** was optimized for batch operation prior to the transfer to continuous operation.

In anticipation of the development of a multistep synthesis in flow, we focused our studies on obtaining a final reaction concentration of 0.2 M, which directly matches with the 0.2 M cyclopropane solution that was employed for the optimized continuous flow homo-Nazarov cyclizations, in order to obtain a final concentration of 0.1 M on the cyclization step. The results are as summarized in Table 5-4. At loadings of 1.0 mol% Rh_2esp_2, the reaction in acetonitrile at 23 °C requires more than 2 hours to achieve completion, yielding compound **5-5a** in 82% (Table 5-4, entry 1). An increase in the reaction rate was observed when the reaction was heated to 50 °C and the reaction reached completion in 15 min. The product **5-5a** was observed in 73% yield (Table 5-4, entry 3). Raising the diazo **5-3a** from 1.1 to 1.5 equivalence resulted in an increased yield of 89% (Table 5-4, entry 4). Thus, for **5-5a**, the

optimized batch conditions selected for technology transfer to continuous flow were 1 mol% Rh_2esp_2 in CH_3CN (0.2 M) at 50 °C for ~15 min.

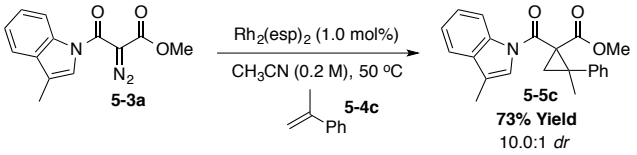
Table 5-4. Batch optimization for cyclopropane 5-5a.



Entry	3a (equiv.)	Temp. (°C)	Time (min)	% Yield[a,b]
1	1.1	23	>120	82
2	1.1	82	5	77
3	1.1	50	15	73
4	**1.5**	**50**	**15**	**89**

a) Isolated yield after chromatography; b) Diastereoselectivities (as determined by ^{1}H NMR) 8.4-8.6:1 *trans:cis dr.*

Using the same cyclopropanation conditions from cyclopropane **5-5a**, cyclopropane **5-5c** was obtained in 73% yield (Scheme 5-2). With two optimized substrates in hand, we next focused our efforts on the transfer from batch to continuous flow.



Scheme 5-2. Formation of cyclopropane 5-5c from diazo 5-3a in batch.

5.3.4 Continuous flow results: Cyclopropanation

The results of the cyclopropanation experiments are shown below in Figure 5-6. The formation of cyclopropane **5-5a** at 50 °C reached full conversion after one residence time (~30 minutes, the flow was decreased by half). Two more samples were collected from the

reactor at residence times two (60 min), and three (90 min). The cyclopropane **5-5a** was isolated and was found to have yields of 83%, 83%, and 78% at residence times one, two, and three, respectively. For cyclopropane **5-5c**, it was found to have yields of 54%, 57%, and 59% at residence times one, two, and three, respectively.

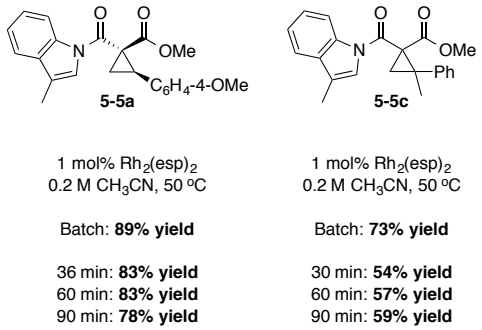


Figure 5-6. Rh_2esp_2-catalyzed cyclopropanation in flow

5.3.5 Tandem Cyclopropanation/Cyclization Sequence

Having the optimized conditions for the cyclopropanation and cyclization reactions to afford compounds **5-6a** and **5-6 c**, both in batch and continuous flow, we then moved to try the tandem cyclopropanation/cyclization sequence. A new coil attachment and pump were added to the continuous flow reactor (see Section 5.2.2) in order to introduce a solution of indium triflate, in a tandem manner, once the cyclopropanation reaction has been completed.

After studying the cyclopropanation and cyclization steps separately, the conditions for the sequenced cyclopropanation/cyclization for compounds **5-6a** and **5-6c** were found without complications (Figure 5-7). In batch, compounds **5-6a** and **5-6c** were obtained in 88% and 91% yield, respectively. When the tandem cyclopropanation/cyclization sequence to obtain compound **5-6a** was translated from batch to continuous flow, hydropyrido[1,2-*a*]indole **5-6a** was isolated in quantitative yields. Compound **5-6a** was found to have yields

of 96%, 86%, >99%, >99%, and >99% at residence times one, two, three, four and five, respectively. Compound **5-6c** was found to have yields of 96%, 86%, >99%, >99%, and >99% at residence times one, two, three, four and five, respectively.

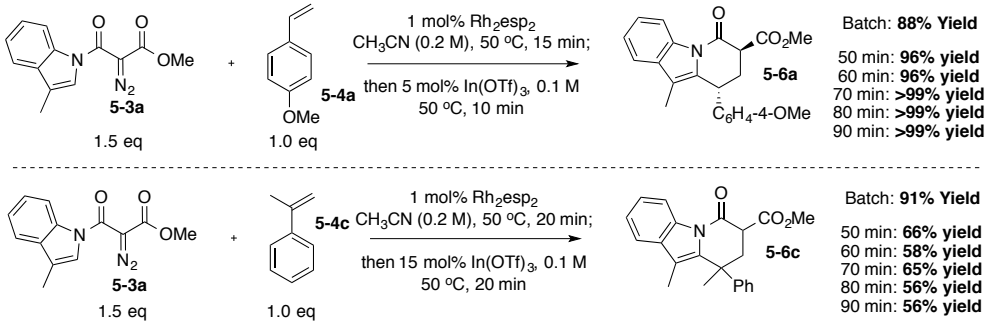


Figure 5-7. Tandem, bicatalytic cyclopropanation-ring-opening cyclization in flow.

5.4 Development of a Strategy that Enables an Efficient One-Pot Tandem Cyclopropanation/Cyclization Reaction via Cooperative Catalysis:

Based on the overwhelming successes of the batch optimization studies for the cyclopropanation and homo-Nazarov cyclization steps, we envisioned the development of a one pot, tandem reaction that would take advantage of cooperative catalysis. In sequential cooperative catalysis,[23] two catalysts, both present at the onset of the reaction, work in unison along a cascade pathway to generate a desired product (Figure 5-8). One catalyst promotes the formation of an intermediate and the second catalyst promotes the reaction of the intermediate into the product.

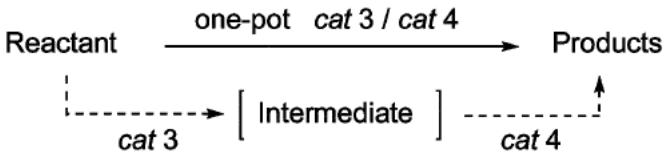
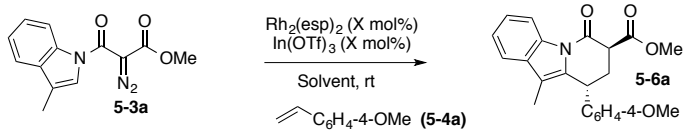


Figure 5-8. Sequential cooperative catalysis.

The France group has previously reported an example of such a reaction for the heteroaromatic homo-Nazarov cyclization.[24] However, only one or two examples provided results superior to the tandem or step-wise processes. This type of catalysis has not been applied to the *N*-acyl cyclopropane systems for homo-Nazarov reactions. We sought to explore the possibility for this reactivity based on the extensive optimization data that was generated (Table 5-5). The first conditions that were examined utilized CH_3CN as the solvent. With an eye ultimately on flow, we sought reactions that could be completed within a short time frame (<30 min). When diazo ester **5-3a** (1.1 equiv) in a solution of CH_3CN was added to a solution of 4-methoxystyrene (1.0 equiv), Rh_2esp_2 (1.0 mol%) and $In(OTf)_3$ (5 mol%), the reaction provided very low conversion to the desired products within 2-3 h (Table 5-5, entry 1). Various byproducts were observed for the reaction. We assume these byproducts are a combination of degradation/unwanted reaction of the carbenoid species and polymerization of the alkene. Adding credence to this hypothesis, when the reaction was heated to 50 ˚C, only degradation products were observed. Regardless of whether the stoichiometries of the various components were changed, only low conversion (<30%) of product **5-6a** was observed.

Table 5-5. Sequential cooperative catalysis study for formation of 5-6a.



Entry	$Rh_2(esp)_2$ (mol%)	$In(OTf)_3$ (mol%)	Solvent	Conc. (M)	Time	% Yield
1	1.0	5.0	CH_3CN	0.2	2-3 h	Trace
2	0.1	5.0	$PhCH_3$	0.2	15-20 min	28
3	0.2	5.0	$PhCH_3$	0.2	15-20 min	trace
4	0.1	10.0	$PhCH_3$	0.2	10-15 min	trace
5	0.1	2.5	$PhCH_3$	0.2	1 h	trace
6	**0.1**	**5.0**	**$PhCH_3$**	**0.1**	**15 min**	**75 (71)**

In contrast to CH_3CN, when toluene was employed as the solvent, some interesting results were obtained. When the 0.1 mol% Rh_2esp_2 and 5.0 mol% $In(OTf)_3$ was employed in toluene at a concentration of 0.2 M, hydropyrido[1,2-*a*]indole **5-6a** was obtained in 28% yield (Table 5-5, entry 2, ~52% yield/step). Changes to the loadings of rhodium or indium failed to provide any tangible amounts of product (Table 5-5, entries 3 to 5). Interestingly, when the concentration was changed to 0.1 M while keeping the rhodium and indium loadings the same [0.1 mol% Rh_2esp_2, 5.0 mol% $In(OTf)_3$], the desired product **5-6a** was obtained in 75% yield (Table 5-5, entry 6, ~87% yield/step). When the reaction was repeated a second time, a 71% yield of **5-6a** was obtained, thus confirming the validity and consistency of the protocol. Thus, we have laid the groundwork for the development of one-pot cyclopropanation/homo-Nazarov cyclizations of alpha-diazoesters via sequential cooperative catalysis. Although this result is highly encouraging in batch, there is a major limitation to the transfer to flow. For the optimized reaction conditions, $In(OTf)_3$ is not fully solubilized in toluene at the 0.1 M concentration. This poses a major problem/challenge for continuous flow due to the inability

of most pumps to handle heterogeneous solutions. This is something that will be addressed by examining other more soluble In complexes or other soluble Lewis acid catalysts.

5.5 Conclusion

In conclusion, we have successfully developed a tandem, bicatalytic continuous flow cyclopropanation-homo-Nazarov-type ring-opening cyclization for the synthesis of hydropyrido[1,2-*a*]indoles. The continuous flow sequence employs CH_3CN as the unifying and industrially-viable solvent and provides high conversions and reaction throughputs on the order of 4-7 g h^{-1} without the need for intermediate purification steps. Reaction times and conversions appear tuneable by modifying the temperature, changing reaction concentration, or by employing different reactor coils lengths/sizes. The tandem reaction also represents a significant synthetic improvement over our previously published two-pot batch protocol. Upon performing the corresponding batch optimization, this process could also be applied to all the diazo chemistry developed in the France Lab.

Also, the development of a one-pot cyclopropanation/homo-Nazarov cyclizations of alpha-diazoesters via sequential cooperative catalysis is also under investigation, with preliminary results of 75% yield for compound **5-6a**.

5.6 Experimental

5.6.1 General methods

Chromatographic purification was performed as flash chromatography with Dynamic Adsorbents silica gel (32-65 μm) or preparative thin-layer chromatography (prep-TLC) using silica gel F_{254} (1000 μm) plates and solvents indicated as eluent with 0.1-0.5 bar pressure. For

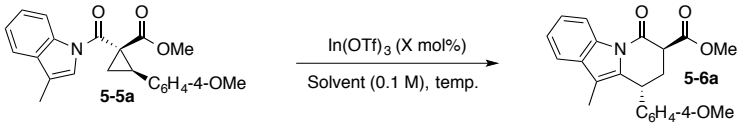
quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F_{254} TLC glass plates. Visualization was accomplished with UV light. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 MHz spectrometer, or Bruker 400 MHz and 500 MHz spectrometers with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). A Shimadzu GC‐2010 gas chromatograph fitted with a Supelco PTA‐5 (30m x 0.32 mm x 1.00 μm, length x inside diameter x film thickness) capillary column was used to analyze the products of the tandem reactions in flow. All compounds synthesized matched our previously reported characterization data.[14]

5.6.2 Experimental procedures

a. Batch optimization for ring-opening cyclizations

General Cyclization Procedure: An oven-dried round bottom flask was charged with $In(OTf)_3$ (0.5 to 30 mol%) and the indicated solvent (2.0-2.5 mL). Once the mixture was heated to the indicated temperature, a solution of the cyclopropane **5-5** (1.0 equiv.) in the indicated solvent (2.3-2.5 mL) was added in one shot, keeping the reaction mixture at the indicated temperature. The reaction was monitored by thin layer chromatography (TLC) every 15 minutes until the starting material could no longer be detected. The reaction was then quenched with 1.0 mL of water and the ^{1}H NMR of an aliquot was acquired to determine the conversion. The product was extracted from the aqueous phase with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. The organic layers were concentrated for silica gel flash column chromatography.

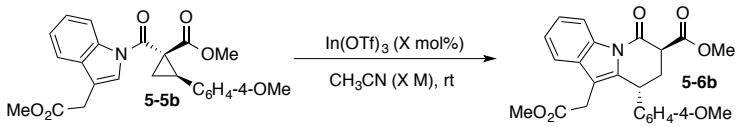
Table S5-1. Complete solvent screen for conversion of 5-5a to 5-6a.



In(OTf)$_3$ (mol%)[a]	Solvent	Temp. (°C)	Time	% Conversion[b]
30	CH_2Cl_2	23	< 15 min	>99
30	THF	23	12 hrs	>99
30	MTBE	23	9 hrs	>99
30	MeOH	23	24 hrs	--[c]
30	*i*PrOH	23	24 hrs	--c
30	$PhCH_3$	23	<15 min	>99
30	$(CH_3)_2CO$	23	30 min	>99
30	EtOAc	23	15-30 min	>99
10	EtOAc	23	12 hrs	90
10	EtOAc	77	20-30 min	>99
5	EtOAc	23	24 hrs	<10
5	EtOAc	77	30-40 min	95
30	CH_3CN	23	<15 min	>99
10	CH_3CN	23	<15 min	>99
5	**CH_3CN**	**23**	**15 min**	**>99 (96)**[d,e]
1	CH_3CN	23	20-30 min	95
1	CH_3CN	82	15 min	95
0.5	CH_3CN	23	18 hrs	90

a) Reactions were run with cyclopropane **5-5a** (0.3 mmol scale, 1 equiv.) and In(OTf)$_3$ (X mol %) in the indicated solvent (0.1 M) at room temperature; b) Determined by ^{1}H NMR; c) No reaction observed after 24 h. d) Number in parentheses represents isolated yield after chromatography; e) Diastereoselectivities (as determined by ^{1}H NMR) range from 1.9-2.3:1 *trans*:*cis dr*.

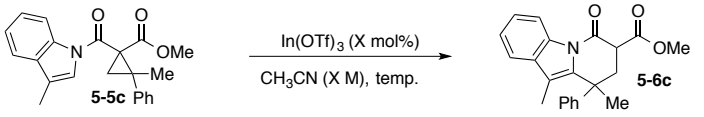
Table S5-2. Cyclization of 5-5b.



In(OTf)$_3$ (mol%)[a]	Conc. (M)	Time[b]	% Yield[c,d]
5	0.5	5 min	85
5	**0.1**	**10 min**	**90**
1	0.5	15 min	71

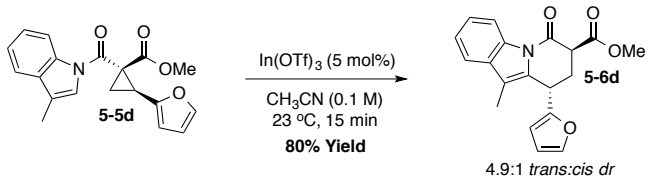
a) Reactions were run with cyclopropane **5-5b** (0.3-0.75 mmol scale, 1 equiv.) and In(OTf)$_3$ (X mol %) in CH_3CN (X M) at rt; b) Time to reach completion as determined by TLC; c) Isolated yield after column chromatography; d) Diastereoselectivities (as determined by ^{1}H NMR) range from 1.7-1.9:1 *dr*.

Table S5-3. Cyclization of 5-5c.



In(OTf)$_3$ (mol%)[a]	Conc. (M)	Temp. (°C)	Time[b]	% Yield[c]
5	0.1	23	24 h	--[d]
10	0.1	23	15 min	24
10	0.2	23	20 min	32
10	0.5	23	20 min	42
15	*0.2*	23	20 min	42
30	0.1	23	24 h	--[d] (44)[e,f]
15	0.1	23	24 h	94 (34)[e,f]
15	**0.1**	**50**	**10 min**	**>99**[f]
5	0.1	50	15 min	89[f]

a) Reactions were run with cyclopropane **5-5c** (0.3-0.75 mmol scale, 1 equiv.) and In(OTf)$_3$ (X mol %) in CH_3CN (X M) at the indicated temperature; b) Time to reach completion as determined by TLC; c) Isolated yield after column chromatography; d) Reaction products not isolated; e) Yield in parentheses represent isolated yields after quenching the reaction after 15 min; f) Diastereoselectivities (as determined by ^{1}H NMR) range from 1.1-1.3:1 *dr*.



Scheme S5-1. Cyclization of 5-5d.

b. Continuous flow cyclopropane homo-Nazarov-type ring-opening cyclizations

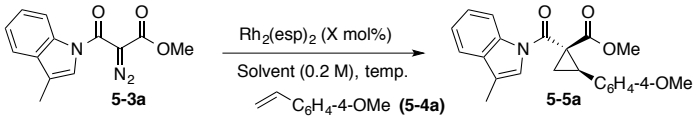
General Procedure: The ring-opening cyclizations were performed as follows: a 0.2 M solution of cyclopropane in acetonitrile was mixed with a 0.01 M solution of In(OTf)$_3$ in CH_3CN. Each reciprocating pump was set to 0.984 mL/min in order to yield a total flow rate 1.968 mL/min and a residence time of 15 minutes. The resulting reaction stream composition was 0.1 M in cyclopropane and 0.005 M In(OTf)$_3$. The composition and flow rates were chosen to directly mimic conditions and reaction time of batch reactions. A sample of the

reactor effluent was collected for one minute into 1 mL of water (to quench further reaction) at every 15 min to establish equilibrium composition and yield. Samples were extracted with dichloromethane, washed with water and evaporated to dryness with a rotary evaporator. Conversions were determined by ^{1}H NMR analysis and yields were calculated by weighing solid residue for each residence time sample.

c. Batch optimization for cyclopropanations

General Procedure: An oven-dried round bottom flask was charged with Rh_2esp_2 (0.1-1.0 mol %), the indicated solvent (2.0-2.5 mL) and the corresponding alkene (1.0-1.5 equiv.). Once the reaction mixture was heated to the indicated temperature, a solution of the alpha-diazo ester **5-3** (1.0-1.5 equiv.) in the indicated solvent (2.3-2.5 mL) was added in one shot, keeping the reaction mixture at the indicated temperature (the diazo solution was preheated for the reactions ran at elevated temperatures). The reaction was monitored via TLC and after complete consumption of the diazo compound, the reaction was quenched with saturated aqueous thiourea and allowed to stir for 30 minutes. Reactions ran in toluene were extracted with EtOAc (2x). The organic layer was washed with brine, dried with Na_2SO_4, concentrated, and column chromatography afforded the desired cyclopropane. For reactions ran in CH_3CN, the solvent was removed, then the reaction mixture was extracted and purified following the same protocol as the reactions ran in toluene.

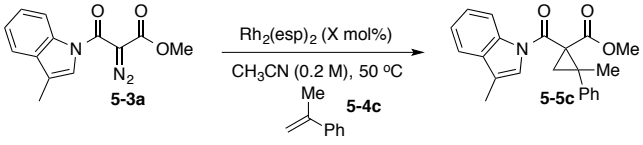
Table S5-4. Formation of cyclopropane 5-5a.



3a:4a Ratio	$Rh_2(esp)_2$ (mol%)	Solvent	Temp. (ºC)	Time[a,b]	% Yield[c,d]
1.1:1	1.0	Toluene	23	< 5 min	86
1.1:1	0.1	Toluene	23	20 min	87
1.1:1	0.5	CH_3CN	23	48 hrs	--[e]
1.1:1	1.0	CH_3CN	23	48 hrs	82
1.1:1	1.0	CH_3CN	82	<10 min	77
1.1:1	0.1	CH_3CN	82	15-20 min	--[e]
1.1:1	1.0	CH_3CN	50	15 min	73
1.3:1	1.0	CH_3CN	50	15 min	83
1.5:1	**1.0**	**CH_3CN**	**50**	**15 min**	**89**
1:1.1	1.0	CH_3CN	50	15 min	74
1:1.3	1.0	CH_3CN	50	15 min	77
1:1.5	1.0	CH_3CN	50	15 min	77

a) Reactions were run with diazo **5-3a** (X equiv.), alkene **5-4a** (X equiv.) and Rh_2esp_2 (X mol %) in CH_3CN (0.2 M) at the indicated temperature; b) Time to reach completion as determined by TLC; c) Isolated yield after column chromatography; d) Diastereoselectivities (as determined by ^1H NMR) ranged from 10.0-12.0:1 *dr*; e) Reaction products not isolated.

Table S5-5. Formation of cyclopropane 5-5c.



3a:4c Ratio	$Rh_2(esp)_2$ (mol%)	Time[a,b]	% Yield[c,d]
1.1:1	1.0	15 min	59
1.1:1	1.0	20 min	70
1.5:1	**1.0**	**20 min**	**73**

a) Reactions were run with diazo **5-3a** (X equiv.), alkene **5-4c** (X equiv.) and Rh_2esp_2 (X mol %) in CH_3CN (0.2 M) at 50 ºC; b) Time to reach completion as determined by TLC; c) Isolated yield after column chromatography; d) Diastereoselectivities (as determined by ^1H NMR) ranged from 7.3-7.5:1 *dr*; e) Reaction products not isolated.

d. Continuous flow cyclopropanations

General Procedure: Using the single step plug flow reactor in Figure 5-2, the cyclopropanation reaction was conducted as follows: a 0.6 M solution of diazoester 2 in CH_3CN (pump 1) was reacted with a solution of 0.004 M $Rh_2(esp)_2$ and 0.4 M styrene substrate in CH_3CN (pump 2). The pumps were set to deliver a volumetric flow rate of 0.49 mL/min each. This provided a reaction mixture that was 0.3 M diazoester, 0.2 M styrene and 1 mol% Rh_2esp_2. In order to quench the catalyst and prevent further reaction upon exiting the reactor, the effluent was quenched into saturated thiourea water solution. Every 30 minutes, a sample of the effluent was collected for 2-3 min, and its weight was recorded and used to calculate the amount of desired cyclopropane product according to equations (1) and (2).

$$yield = m_{iso.}/(\frac{m_{t2}}{m_2} \times m_{styr.} \times \frac{M_{cycl.}}{M_{styr.}}) \qquad (1)$$

$$m_{t2} = \rho_2 \times v_2 \times m_t/(v_1 \times \rho_1 + v_2 \times \rho_2) \qquad (2)$$

Where $m_{iso.}$ is the isolated cyclopropane product for each sample, m_{t2} is the partial weight of each sample fed by pump 2, m_2 is the total weight of solution in pump 2, $m_{styr.}$ is the total weight of styrene in pump 2, $M_{cycl.}$ is the molecular weight of cyclopropane, $M_{styr.}$ is the molecular weight of styrene, ρ_1 and ρ_2 are the densities of solution in pump 1 and pump 2, v_1 is and v_2 are the volumetric flow rates of pump 1 and pump 2, m_t is the weight of each sample.

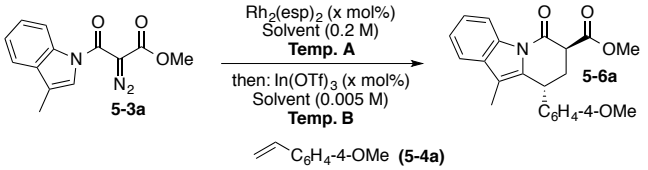
Due to production of N2 during the cyclopropanation reaction, the effluent volumetric flow rate at exit became irregular. To incorporate this irregularity, the flow rate was halved to

increase residence time from 15 to 30 min. Thus, sampling residence times were changed to 36 min, 60 min and 90 min.

e. Batch optimization for tandem cyclopropanation/ring-opening cyclizations

General Procedure: The general cyclopropanation procedure was followed for the first step of the reaction. Once the diazo compound was consumed (monitored via TLC), a solution of $In(OTf)_3$ (in 4.5-5 mL of the indicated solvent) was added, keeping the reaction mixture at the indicated temperature (the $In(OTf)_3$ solution was preheated for the reactions ran at elevated temperatures). The reaction was monitored via TLC and after complete consumption of the cyclopropane compound, the reaction was quenched with saturated aqueous thiourea and allowed to stir for 30 minutes. Reactions ran in toluene were extracted with EtOAc (2x). The organic layer was washed with brine, dried with Na_2SO_4, concentrated, and column chromatography afforded the desired cyclopropane. For reactions ran in CH_3CN, the solvent was removed, then the reaction mixture was extracted and purified following the same protocol as the reactions ran in toluene.

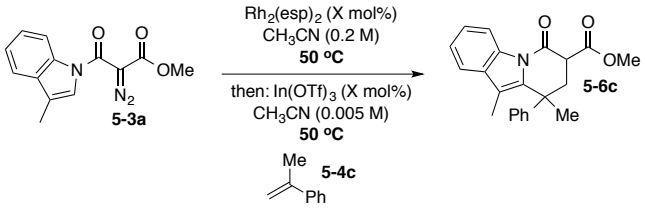
Table S5-6. Tandem reaction to form hydropyrido[1,2-a]indole 5-6a.



3a:4a Ratio[a]	Solvent	Rh2(esp)2 (mol%)	Temp. A (°C)	$In(OTf)_3$ (mol%)	Temp. B (°C)	Time[b] (t_1/t_2)	% Yield[c]
1.1:1	Toluene	0.5	23	5	23	5 min/20 hrs	64
1.1:1	CH_3CN	1.0	82	5	23	5 min/1 h	48
1.1:1	CH_3CN	0.5	82	5	23	5 min/1 h	43
1.1:1	CH_3CN	0.5	50	5	50	40 min/10 min	65
1.5:1	CH_3CN	1.0	50	5	50	20 min/10 min	88
1.5:1	**CH_3CN**	**1.0**	**50**	**2.5**	**50**	**20 min/15 min**	**89**

a) Reactions were run with diazo **5-3a**, alkene **5-4a**, and indicated amounts of Rh_2esp_2 and $In(OTf)_3$ in CH_3CN (0.1 M) at the indicated temperatures; b) t_1 represents time until observed consumption of diazo **5-3a** by TLC, prior to addition of $In(OTf)_3$; t_2 represents the time to reach completion following addition of $In(OTf)_3$; c) Isolated yield after column chromatography.

Table S5-7. Tandem reaction to form hydropyrido[1,2-a]indole 5-6c.



3a:4c Ratio[a]	Rh2(esp)2 (mol%)	$In(OTf)_3$ (mol%)	Time[b] (t_1/t_2)	% Yield[c]
1.5:1	1.0	5	20 min/20 min	33
1.5:1	1.0	15	20 min/20 min	91

a) Reactions were run with diazo **5-3a**, alkene **5-4c**, and indicated amounts of Rh_2esp_2 and $In(OTf)_3$ in CH_3CN (0.1 M) at the indicated temperatures; b) t_1 represents time until observed consumption of diazo **5-3a** by TLC, prior to addition of $In(OTf)_3$; t_2 represents the time to reach completion following addition of $In(OTf)_3$; c) Isolated yield after column chromatography.

f. Tandem, bicatalytic continuous flow cyclopropanation-ring-opening cyclizations

General Procedure: Using the tandem reactor apparatus in Figure 5-3, the tandem, bicatalytic reaction was conducted as follows: a 0.6 M solution of diazoester 2 in CH_3CN (pump 1) was reacted with a mixture of $Rh_2(esp)_2$ catalyst (0.004 M), styrene (0.4 M) and internal standard

p-xylene (pump 2) in reactor 1. *p*-Xylene was used in tandem reactions as internal standard to keep track of the amount of styrene, and therefore to quantify the product yields. Due to production of N_2 in the cyclopropanation reaction in reactor 1, the effluent of this reactor with irregular volumetric flow rate is then mixed with a feed stream (pump 3) of $In(OTf)_3$ (0.005 or 0.015 M) by passing through a 6 mL mixing bed packed with 2 mm borosilicate glass beads. The mixed stream is then fed into reactor 2. Heating was provided via heat tape wound about the reactor coils and controlled with Digisense temperature controllers. Water was used to quench the $In(OTf)_3$ catalyst and prevent further reaction upon exiting the reactor 2. At the end of the first residence time (50 min), the mixture effluent was collected for 2 to 3 minutes (5 to 6 ml) into 4 mL of water every 10 minutes. The organic phase in the sample was extracted with 5 ml dichloromethane for three times and then diluted to 25 ml. The concentration of *p*-xylene in the 25 ml solution was determined by gas chromatography/flame ionization detector (GC-FID).

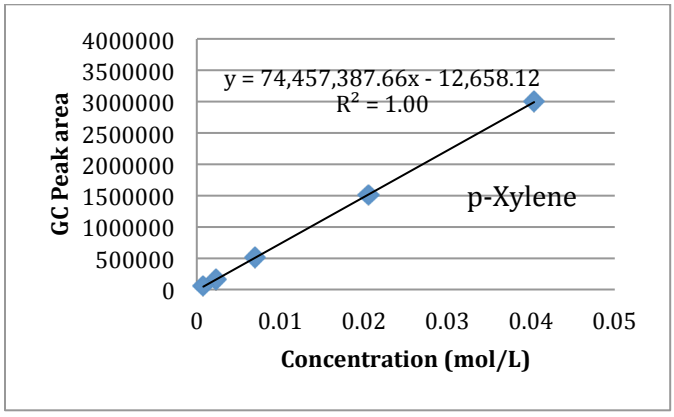


Figure S5-1. GC-FID calibration curve for *p*-xylene for tandem reactions.

5.7 References

1. a) Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.*, **2012**, *354*, 17-57; b) Malet-Sanz, L.; Susanne, F. *J. Med. Chem.* **2012**, *55*, 4062-4098.
2. Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry D. A.; Stefaniak, M. *Green Chemistry*, **2008**, *10*, 31-36.
3. Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, Jr., J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.*, **2007**, *9*, 411-420.
4. Vaccaro, L.; Lanari, D.; Marrocchi, A.; Strappaveccia, G. *Green Chem.*, **2014**, *16*, 3680-3704.
5. Wiles, C.; Watts, P. *Green Chem.* **2012**, *14*,38-54.
6. Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675-680.
7. Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013**,*42*, 8849-8869.
8. Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K. *Chem. Commun.* **2006**, 2566-2568.
9. Riva, E.; Rencurosi, A.; Gagliardi, S.; Passarella, D.; Martinelli, M. *Chem. Eur. J.* **2011**, *17*, 6221-6226.
10. Jimenez-Gonzalez, C.; Poechlauer, P.; Broxterman, Q. B.; Yang, B.-S.; am Ende, D.; Baird, J.; Bertsch, C.; Hannah, R. E.; Dell'Orco, P.; Noorman, H.; Yee, S.; Reintjens, R.; Wells, A.; Massonneau, V.; Manley, J. *Org. Process Res. Dev.* **2011**, *15*, 900-911.
11. Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. *Synlett* **2006**, 427-430.

12. Murray, P. R. D.; Browne, D. L.; Pastre, J. C.; Butters, C.; Guthrie, D.; Ley, S. V. *Org. Process Res. Dev.* **2013**, *17*, 1192-1208.

13. Snead, D. R.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2015**, *54*, 983-987.

14. Patil, D. V.; Cavitt, M. A.; Grzybowski, P.; France, S. *Chem. Comm.* **2011**, *47*, 10278-10280.

15. Cavitt, M. C.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804.

16. Di Grandi, M. J. *Org. Biomol. Chem.* **2014**, *12*, 5331-5345.

17. De Simone, F.; Saget, T.; Benfatti, F.; Almeida, S.; Waser, J. *Chem. Eur. J.* **2011**, *17*, 14527-14538.

18. Franca, P. H. B.; Barbosa, D. P.; da Silva, D. L.; Ribeiro, E. A. N.; Santana, A. E. G.; Santos, B. V. O.; Barbosa-Filho, J. M.; Quintans, J. S. S.; Barreto, R. S. S.; Quintans, L. J.; de Araujo, J. X. *BioMed. Res. Int.* **2014**, 375-423.

19. Gupta, L.; Talwar, A.; Chauhan, P. M. S. *Front. Med. Chem.* **2012**, *6*, 361-385.

20. Kittakoop, P.; Mahidol, C.; Ruchirawat, S. *Curr. Top. Med. Chem.* **2013**, *14*, 239-252.

21. Singla, R.; Negi, A.; Singh, V. *PharmaTutor Mag.* **2014**, *2*, 76-82.

22. Aponte-Guzmán, J.; Shenje, R.; Huang, Y.; Woodham, W. H.; Saunders, S. R.; Mostaghimi, S. M.; Flack, K. R.; Pollet, P.; Eckert, C. E.; Liotta, C. L.; France, S. *Ind. Eng. Chem. Res.* **2015**, *54*, 9550.

23. Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev*. **2004**, *33*, 302.

24. Phun, L. H.; Patil, D. V.; Cavitt, M. A. *Org. Lett*. **2011**, *13*, 1952.